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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES.

THE NATURE AND MODE OF REGULATION OF GLOMERULAR FUNCTION.*

By A. N. Richards, Ph.D.,

PHILADELPHIA.

(From the Laboratory of Pharmacology of the University of Pennsylvania Medical School.)

The literature of investigations of the function of the kidney reveals two distinct types of work. In one the kidney has been studied as one unit in the aggregate of organs which makes up the animal body—a unit upon the normality of whose function the welfare of the rest of the body depends. In such study the reactions of the kidney as a whole to changes in the conditions under which it works have been determined and expressed in terms of change in amount and character of urine eliminated. Such study has had the highest importance in the development of conceptions of the rôle which the kidney plays in the maintenance of that constancy of composition of body tissues and fluids which is essential for health; and it has directly aided the physician in practical problems in which he is required to detect and to evaluate abnormalities of renal function encountered in disease. For the purpose of such study it is not at all inconsistent with the requirements of scientific inquiry to regard the kidney itself as a unit, to speak figuratively, as a sieve with blood pouring into one opening and urine issuing from another—a sieve whose inlet, outlet and size of

* A lecture on the Mary Scott Newbold Foundation, delivered before the College of Physicians of Philadelphia on April 21, 1925.

mesh are exquisitely adaptable to the necessities of the organism as a whole. Such expressions as "renal permeability," "renal threshold" are current illustrations of this implication.

In the second group of investigations are to be found those studies of kidney function in which effort is made to analyze the fashion in which the kidney performs its work. The basis of these efforts is recognition of the fact that the kidney, far from being a homogeneous structure, is a compact assemblage of millions of minute structures, and each of these, in turn, is composed of a number of highly differentiated parts; and that these minute parts are functionally adjusted with incredible nicety not only to each other but to the activities of the rest of the body as well. It is the aim of the student who wishes to analyze the function of the kidney on this basis to cultivate sufficient imagination and skill in experimentation to accomplish the identification and separate study of the functions of each different structure of which the kidney is composed, to the end that eventually he may obtain a conception of the workings of the kidney as a whole which includes an understanding of the contribution which each element of the kidney supplies. The results of such study are not apt to yield direct and immediate assistance to the physician in the solution of practical problems; but if they lead to sounder conceptions of the fundamental processes of kidney function they can hardly fail to furnish the basis for greater discernment and better judgment in practical tasks which concern it.

The work which I propose to describe belongs in this second category. It has been proceeding for ten years in the laboratory of which I am in charge and it is still in progress. The work would not have been possible except for the collaboration of a number of colleagues whose names I shall mention in appropriate connections and to whom the highest credit should be given.

The title of this account, "The Nature and Mode of Regulation of Glomerular Function," intimates the restriction of our discussion to one small part of the kidney. I think that we have enough information concerning glomerular function to warrant this; and I wished to make this choice of title implicitly express my conviction that until we can arrive at a reasonably accurate understanding of the part played by glomerular structures in urine formation, our footholds for progress toward elucidation of the function of the renal tubules are insecure. The literature of renal physiology contains an enormous amount of speculation, owing to the fact that intricacy of structure has made unambiguous experiment difficult. When we shall have designed and made unambiguous experiments on the glomerulus of such sort as to remove or lessen materially the necessity of speculation concerning its function we shall surely find that the speculative element in a consideration of tubular function is diminished.

Bowman,[1] in 1842, was the first who satisfactorily demonstrated that the tuft of capillaries which we call the glomerulus is actually inserted into the end of the tubule, the modified wall of which is expanded to form the capsule in which the tuft is enclosed. Hence the intracapsular space is the beginning of the lumen of the renal tubule. He advanced the view that fluid leaves the blood as it passes through the glomerular capillaries, and that this fluid, washing the inner surface of the cells composing the tubule, carries away the products of their secretory activity. He conceived the glomeruli to act as an automatic "sluice" by which water, salts of which the body was not in need, and many foreign substances were eliminated. Experimental evidence supporting the correctness of this view that fluid issues from the glomerular capillaries was supplied by Nussbaum[2] in 1878; indirect evidence was adduced by Brodie and Mackenzie[3] in 1914. But in 1922 and 1923 W. N. F. Woodland[4] published a series of studies of the frog's kidney which led him to the view that the glomerulus has nothing whatever to do with the actual production of urine but acts rather as a pressure-reducing valve in the circulation to the tubules, by which he conceives the entire urine to be secreted. It is not necessary to enter upon a detailed critique of Woodland's work. But since the question raised is fundamental to the discussion which I am beginning, it must of necessity be answered. The answer which, I think, completely controverts Woodland is found in an observation by Wearn[5] made in our laboratory. By methods presently to be described, we taught ourselves to penetrate Bowman's capsule in the frog's kidney with a very finely pointed capillary pipette. By this means fluid from the capsule could be collected continuously for many hours. When blood ceased flowing through the glomerular capillaries fluid ceased rising in the capillary tube, though interruption of glomerular flow in the frog does not entail interruption in flow through vessels supplying tubules. In one experiment, by accident rather than by design, the opening from capsular space into the lumen of tubule was closed by a droplet of mercury injected into the capsular space. Accumulation of glomerular fluid in the pipette, previously slow and unsatisfactory, now became rapid. This observation demonstrates in conclusive fashion the correctness of Bowman's assumption and the fallacy of Woodland's.

Having proof that fluid which is eventually to become urine leaves the blood during its passage through the glomerular capillaries, we may take up the question of the nature of the responsible process involved. Examination of the arrangement of glomerular capillaries in contrast with capillaries in other areas shows certain definite differences. In the glomerulus a single arteriole, the vas afferens, breaks abruptly into a number of capillaries (in the frog three primary and six secondary branchings; in mammals, from the drawings of Bowman, many more). In the abrupt transition from

afferent vessel to glomerular capillaries the cross-section of the vascular bed increases many times; no such abrupt increase is found in other vascular areas. In the glomerulus the capillaries reassemble into the efferent vessel, smaller in diameter than the afferent; whereas in other vascular areas the efferent veins are larger than the arteries. Further, the length of the smaller arterioles leading to the glomerular system of capillaries is less than is length of the arterioles leading to the capillaries in other tissues, and as a result the head of pressure in blood reaching the glomerular capillaries must be higher than that in blood reaching other capillary areas.

Such considerations as these led Ludwig to the view that the blood pressure in the capillaries of the glomerular tuft is higher than in other regions; and that in consequence a protein-free filtrate is pressed out of the plasma through the capillary wall.[6] This is the filtration theory. It received support from experiments in which a parallelism was shown to exist between urine formation and renal arterial blood pressure. After general acceptance for some thirty years it was effectively attacked by Heidenhain,[7] on three chief grounds: (1) That certain dyes, injected into the circulation, appear to be eliminated by the tubules and not by the glomerulus, as judged by the appearance of sections of the kidney made after death; (2) that partial obstruction of the renal vein—a measure conceived to be capable of increasing pressure in the glomerular vessels—does not increase urine; (3) that the amount of glomerular filtration necessary to unload from the blood the amount of urea which is eliminated daily by the kidney was incredibly large when compared with his estimate of daily volume of blood flow through the renal vessels. These apparently insuperable objections led Heidenhain to substitute for the filtration theory an hypothesis which ascribed to the epithelium known to envelop the glomerular capillaries a power of causing the withdrawal of a fluid from the blood passing through these capillaries. Ludwig, in advancing the filtration theory, was obliged to attach to it a theory that reabsorption occurs in the tubules. Heidenhain, denying filtration, saw no need of a reabsorptive process, but saw in his results evidence of a secretory process in tubule cells. Following Heidenhain's work faith in the filtration hypothesis diminished. It was revived, however, some twenty-five years later by the work of Starling,[8] in which was demonstrated the striking coincidence between the osmotic pressure of the plasma colloids and the values which he was able to assign for the minimal glomerular capillary pressure at which urine was formed. As late as 1910, however, opinions held by competent students of kidney function were divided on this question.[9]

The question is one which is of a great deal of interest to one who is obliged to interpret the diuretic action of drugs, for the

reason that the interpretation of such action can be no more convincing than is his conception of the processes which the drugs affect. The beginning of the experiments which we have made was undertaken for the purpose of discovering whether the secretory theory of renal function was better suited to explain the action of caffein upon the kidney than was the filtration theory. An apparatus was made by Drinker and myself,[10] by which blood could be passed through the living kidney of a rabbit *in situ* in a manner which closely resembled that in which blood is pumped by the animal's heart, but with one difference, that the mechanical pump which we arranged was constant in its output regardless of the state of dilatation or constriction of the vessels through which the blood was pumped. Plant and I applied the apparatus to the study of the action of caffein on the rabbit's kidney *in situ*.[11] It was our thought that if caffein were not capable of producing diuresis under conditions which did not permit alteration in blood flow through the kidney, the conclusion would be justified that the normal diuretic action of caffein is a vascular one. The result showed, however, that caffein was able to produce marked diuresis under the conditions stated, and for a time, therefore, we were inclined to regard our results as in harmony with the secretory theory of urinary production.*

But during these experiments it became obvious that we had in our hands a method for an attack upon the problem of the nature of the forces which are responsible for urine formation more direct than any previously available. We had found it possible to maintain the activity of the living kidney with an artificial and controllable circulation of blood through its vessels. It was easily possible to vary the pressure within this artificial circulation without at the same time necessarily influencing the volume of blood flow through the organ per minute. Hence it appeared possible to test the validity of the filtration hypothesis by keeping all recognizable conditions constant with one exception, viz: pressure of blood flowing through its vessels. The experiment was made many times with the uniform result that under conditions which completely prevented an increase in blood flow through the kidney, any considerable increase in pressure was associated with a parallel increase in urinary output.[12] The means by which pressure was raised in these experiments were stimulation of the splanchnic nerve, injection of adrenalin into the circulation and partial obstruction of the renal vein. None of those agencies commonly causes diuresis in the intact animal, because they all lessen the blood flow

* The explanation which we now assign to the diuretic effect of caffein under these conditions is to be found in the experiments on pages 793, 795, 796. They provide reasons for believing that caffein caused increase in glomerular capillary pressure and in number of glomerular capillaries through which blood was flowing; hence it increased glomerular filtration.

in the renal vessels. In our experiment blood flow was not diminished because of the efficiency of our pump, and the relationship between renal blood pressure and urine flow was clearly revealed.

For the first time indubitable evidence was gained that alterations in pressure alone in the renal circulation were responsible for alterations in urinary output, and the experiments may be regarded as the most direct evidence in support of the filtration hypothesis available at the time they were made. By a similar method Dreyer and Verney,[13] in Starling's laboratory, have recently obtained similar results.

My reason for having introduced into this discussion an account of these old experiments is that their results, decisively confirmatory of the observations and reasoning of Ludwig's followers and decisively refuting one of Heidenhain's chief objections, gave us a conviction of the essential soundness of the filtration hypothesis which subsequent experience has not shaken; and they provided suggestions for the design of further experiments which otherwise would not have occurred to us.

In the experiments which immediately followed these, evidence was obtained bearing upon the regulation of glomerular function. These I shall presently describe. A further outcome has been the design of two series of experiments which bear, the one indirectly, the other directly, upon the nature of the glomerular process. This work was based upon the observation which had been made by Dr. Schmidt and myself, that it is possible to apply, after the manner of Krogh, methods of direct illumination to the kidney of the frog with the result that the glomerular vessels and the blood flowing through them becomes easily accessible to direct microscopic vision. Through the work of Barbour, Kite and, more recently, Chambers'[14] methods have been developed for microdissection and microinjections. Professor Chambers, of Cornell, has been able to make capillary pipettes of such extreme fineness that, using a mechanical manipulator of his design, it has been possible to inject foreign substances into the protoplasm of living cells. His demonstration in Philadelphia (1921) excited me to the belief that instruments of this type might become valuable as aids in the solution of a number of problems which concern the behavior of the renal vessels. Dr. Wearn, learning of this thought, transmuted it into the suggestion that by means of such a pipette it might be possible to enter the capsule of Bowman and withdraw the fluid as it collected there, with the hope of subjecting it to study.[15] Our joint efforts resulted in the construction of a simple apparatus by means of which a slender pointed tube could be introduced into the intracapsular space and the glomerular fluid collected. Refinements of current methods of testing were introduced so that the minute quantities of fluid available could be subjected to accurate qualitative tests. The filtration theory of Ludwig's states

that as a result of pressure in the intraglomerular capillaries a protein-free filtrate from plasma passes through the walls of the glomerular capillaries into the space within Bowman's capsule. Our first task, after sufficient manipulative skill had been cultivated, was to test the fluid so obtained for protein. In some fifteen experiments the acetic acid-potassium ferrocyanid test was applied with negative results. Similarly tested a 1 to 100 dilution of frog's plasma gave unmistakable reaction. In other experiments the glomerular fluid was examined for chlorids and in still others for sugar. The urine of the frog kept in fresh running water contains only a faint trace of chlorid (as a rule not more than 0.05 per cent), and if the frog is kept for a day or two in distilled water the urine became completely chlorid-free as judged by the usual test. The glomerular fluid taken from Bowman's capsule of such a frog contains chlorid in impressive quantity.

The bladder urine of frogs, kept under ordinary conditions, contains no sugar detectable by Fehling's solution. The glomerular fluid, however, always reduces Fehling's solution when drawn from frogs whose blood contains detectable amounts of sugar. In our first experiments, made during the months of November and December, no reducing power could be detected in glomerular fluid, but when the blood of these frogs was examined by McLean's method sugar was found to be absent. On repeating the experiment during these months with frogs which had been injected subcutaneously with small amounts of glucose unmistakable reduction tests were obtained in the glomerular fluid. If sugar was injected in sufficient quantity to establish a blood-sugar concentration of 0.066 per cent or more, then sugar appeared in the bladder urine, but in such instances the degree of reduction by the glomerular fluid was decidedly greater than that by the bladder urine.

These experiments, then, revealed by direct tests the absence of protein and the presence of chlorid and of sugar in the fluid leaving the blood stream flowing through the glomerular capillaries, and are completely in accord, in so far as they go, with the demands of the filtration theory. They contain incontestable proof of the reality of reabsorption within the tubules, and provide the basis for further argumentative support of the view that the glomerular function is a physical rather than a "vital" or "secretory" one. Frogs, as we keep them in our tanks, get little or nothing to eat, and living in fresh water their supply of salts is extremely restricted. If they are to survive, they must retain their bodily store of salt and their nutrition is certainly largely dependent upon conservation of the carbohydrates in their tissues. The experiments show that the glomerular process is one which is not adapted to these conservations and that the escape of chlorid and of sugar which takes place there in these animals, disastrous if uncorrected, is actually corrected by the activity of the epithelium lining the

tubules. Such lack of adaptation to the needs of the organism is not commonly encountered in the case of processes which we designate as vital or secretory and may be regarded as indirect evidence that the glomerular process is a physical one.

Another aspect of this matter, however, has become evident as the result of a further series of experiments designed to secure information of the quantitative composition of glomerular fluid in comparison with blood plasma and bladder urine. At first it seemed hopeless to attempt to subject amounts of fluid ranging from 1 to 5 mg. in weight to the various manipulations which are involved in any quantitative procedure. The question, however, is so fundamentally important, from the standpoint of our conception of renal function, that it warranted extraordinary effort. Prof. Theodore Richards, of Cambridge, in his study of the atomic weights of sodium and chlorin, introduced the nephelometric method of estimating silver chlorid in extremely small amounts.[16] We spent months in practice with his method as applied to minute amounts of known NaCl solutions, and at the end of a distressing period of probation were consistently able to estimate amounts of NaCl of the order of 0.01 mg. contained in 0.002 cc of water, with a degree of accuracy not far removed from that which obtains in ordinary quantitative work. The average error in the last six consecutive control estimations was 2.3 per cent.

We applied this method to the fluid taken from Bowman's capsule of frogs.[17] In 3 experiments the figures for glomerular sodium chlorid were so nearly identical with those for plasma sodium chlorid from the same frogs (3 to 9 per cent higher), that one could well believe that the demands of the filtration theory as currently accepted were satisfied within experimental error. But in 7 experiments the discrepancy was too great to be accounted for by experimental error. In 5 of these glomerular Cl was higher than plasma Cl by 17 to 31 per cent of the latter; in 2 by 49 and 100 per cent respectively.

In another series of experiments a partially successful attempt was made to estimate urea in glomerular urine. The results are not so numerous and we do not regard them as so accurate as those of Cl. They indicated a decidedly greater concentration of urea in glomerular urine than in plasma.

We see an intimation in these results that the current conception of filtration as derived from filter paper or other inanimate material may require modification when it is transferred to the process of of filtration as it may be going on through the walls of microscopic tubes consisting of living capillary endothelium covered by a tenuous layer of epithelium. It may be suggested that these figures indicate glomerular "secretion." I do not think that this is the case. They rather show the necessity of a further scrupulous investigation of the fashion in which a physical process may be

modified when it takes place through the living walls of tubes of capillary size.

The information which has already been presented may be summarized as follows:

Direct evidence has been described showing that fluid issues from the blood during its passage through the glomerular capillaries. Under favorable conditions the rate of issue may be disproportionately large in comparison with the rate of elimination of urine from the whole kidney. These facts correspond completely with Bowman's assumption and with the theory of Ludwig and disprove the recent contentions of Woodland.

Such fluid, collected under the most favorable experimental conditions, contains no protein—a fact which is directly opposed to the recent hypothesis of deHaan,[18] whose work led him to conclude that colloids must normally be eliminated in the glomerulus and reabsorbed in the tubule. It contains both sugar and chlorid, while urine simultaneously collected from the whole kidney contains none. This shows a lack of adaptation of the glomerular process which requires correction, and this is accomplished by reabsorption of these substances during passage of the glomerular fluid through the tubules. This lack of adaptation is regarded as indirect evidence in support of the hypothesis that the glomerular function is physical rather than "secretory," filtration rather than secretion.

Under special conditions of experimentation it has been proved that urine elimination increases or decreases with increase or decrease in pressure in the renal bloodvessels, all other conditions so far as known remaining constant. On the assumption, warranted by anatomic considerations, that the effective site of action of pressure is the glomerulus, this fact affords strong support for the filtration theory.

Quantitative estimation of the chlorid content of the glomerular fluid in some instances is in harmony with the filtration theory; but exceptions to this statement have been encountered which indicates the necessity for a study of the fashion in which capillary forces and vitality of the glomerular membranes may influence the filtration process.

In a discussion of the mode of regulation of glomerular function it is vital to keep in mind the fact that the tuft of glomerular capillaries is interpolated between two vessels having the characteristics of arterioles. The afferent vessel is commonly described as having a diameter greater by one-half than that of the efferent vessel. Both are supplied with nerves which terminate upon the muscle cells contained in the wall. Whether nerves penetrate the capsule and make connection with the glomerular capillaries may be regarded as uncertain, though a statement to this effect is contained in the writings of the anatomist Smirnow.[19]

In the experiment which I have previously described in which the rabbit's kidney was perfused with blood at a constant rate and in which increase of pressure was found to be associated with increase in urinary output, the opportunity presented itself for a closer examination of the vascular reactions involved.[20] The experiment was repeated with the rabbit kidney, excised from the body and placed in an apparatus (oncometer) designed for recording changes in its size. After perfusion had begun, small amounts of adrenalin were added to the blood, entering the renal artery. Constriction of bloodvessels occurred, as was shown by prompt and decisive rise in perfusion pressure; but at the same time the size of the kidney increased. The conditions of the experiment were such that this increase could have been due only to dilatation of vessels within the kidney. Thus we were confronted with the paradoxical coincidence of vascular constriction and vascular dilatation in the same organ. Similar experiments were made with other organs of the body—legs and intestine—and in these the increase in pressure caused by adrenalin was invariably associated with diminution in size of the organ perfused. If now it is recalled that the renal circulation differs from that in other structures in that the distensible glomerular tufts are inserted between two contractile vessels, an explanation of this paradox suggests itself. The conditions of the experiments were such that constriction of the afferent vessel could have little or no effect upon the volume of blood entering the vessels of the glomeruli; but constriction of the efferent vessels would inevitably cause increase in pressure in the capillaries proximal to it, despite the fact that no decrease in total amount of blood flowing through the kidney could have occurred. Here for the first time, in so far as my knowledge goes, was encountered experimental evidence of the contractility of vessels on the distal side of the glomerular tuft and the suggestion was obvious that we were dealing with a mechanism which is normally concerned in the regulation of intraglomerular pressure, and therefore of glomerular function.

The suggestion had been specifically made by others[21] that glomerular pressure may be subject to regulation by the relative diameters of the afferent and efferent vessels, but up to this time the question had not become accessible to experimental approach.

In order to relieve our experiments of the stigma which is commonly attached to perfusion experiments in which reduction of variables is secured at the expense of normality of conditions, we planned a series of experiments based upon this thought: The efferent vessel is by common consent smaller than the afferent vessel; an equal degree of vasoconstriction involving the two vessels alike could be expected to produce a greater increase in frictional resistance in the smaller vessel than in the greater. Hence if one could select a dosage of a substance whose action included

constriction of renal arterioles of exactly the suitable degree of magnitude, he might expect to demonstrate a greater degree of obstruction in the efferent vessel than in the afferent, and the expected manifestations of such action would be a coincidence of slight increase in general aortic pressure, diminution in volume of blood flowing through the kidney, increase in size of the kidney and increase in urinary output. After many trials a few experiments have been successfully carried through in which we think the technical demands of the problem were successfully met, and the results completely correspond with the hypothesis on which the experiment was based.[22] In eviscerated rabbits minute dosage with adrenalin, with pituitary extract and with barium chlorid, gave rise to the coincident events upon which I have laid emphasis.

While we were unable to imagine another explanation equally acceptable, an intense desire was aroused for finding another method of test of the hypothesis. It was this desire which led me to think that it might be possible to subject the frog's kidney to methods which permit direct microscopic observation. If such method should prove successful we might obtain direct visual evidence that constrictor substances acting in high dilution produce a greater degree of constriction of the efferent than of the afferent vessel. I invited Dr. Schmidt to collaborate with me in the effort to apply the methods which were at that time being developed by Professor Krogh in other connections, and we soon discovered that it was a relatively simple matter to subject the glomerular circulation of the frog to direct inspection.[23] So far as I know, this had not been previously successfully accomplished. Our first experiments were designed to discover whether the intravenous injection of minute amounts of adrenalin were capable of causing an enlargement of the glomerular tuft in a manner compatible with the conditions which I have presented. The results in the main were favorable to our conception. In many experiments the introduction of 0.001 mg. of adrenalin caused flow of blood through the glomerular channels to be retarded, and caused measurable increase in the diameter of the capillary tuft. This was regarded as evidence that the efferent vessel contracted. We could not subject the efferent and the afferent vessels to direct measurement, because as a rule their outlines were obscured by overlying tissue.

While this result was in harmony with those of the mammalian experiments, we conceived one source of possible error as attached to it. Adrenalin not only affects the vessels of the frog's kidney but also those of other tissues; it also increases the activity of the heart. The effect, therefore, which we observed might conceivably be the result of increased blood supply to the kidney consequent upon cardiac stimulation and increased aortic pressure. It was therefore incumbent to design a perfusion experiment with the frog's kidney similar to that which had been made with the rabbit,

so that the blood flow through the frog's kidney should be constant regardless of the state of dilatation or constriction of the renal vessels. That there are technical difficulties to be encountered in such an experiment is obvious and a successful attempt to overcome this has only recently been made in collaboration with Mr. Bradley and Dr. Barnwell: Two syringes of identical caliber were filled with the whole blood from other frogs and arranged so that the contents of either could be driven at constant rate through the vessels of the kidney *via* the renal arteries. Adrenalin to make a concentration of 1 to 500,000 was added to the blood in one syringe. The animal was adjusted on the stage of a microscope provided with a photomicrographic camera so that photographs of glomerular tufts could be taken at frequent intervals during the course of the experiment. Substitution of blood containing this minute amount of added adrenalin for blood containing none caused an unmistakable increase in the size of the glomerular tufts which were under observation. Simultaneous records of pressure in the renal artery and of the amount of blood issuing from the renal vein showed the characteristic constriction of renal vessels but without any diminution in the rate of passage of blood through the entire organ. The objections which had been made to the acceptance of our conclusions from the experiment on the intact frog seem, therefore, to have been overcome, and we regard this as strong evidence that an increase in intraglomerular pressure may result from constriction of the efferent vessel.

In these experiments attention has been concentrated upon effects which may be produced by minute amounts of the substance adrenalin. We were not primarily interested in the action of this substance as a drug; its great interest for us lies in the fact that it is a hormone which normally circulates in the blood and takes part, we believe, in circulatory adjustments of the most exquisite kind. Its action on bloodvessels, as is well known, is identical with that of sympathetic nerve stimulation, and hence in exposing the intricacies of its action we gain information which is applicable also to nervous control of the renal vessels.

These experiments provide the basis for thinking that very small amounts of adrenalin or very slight stimulation of sympathetic nerves to the kidney may increase intraglomerular pressure by more effective action on efferent than on afferent vessels; while larger amounts of adrenalin or more intense nerve stimulation, by causing constriction of both, lessen both glomerular pressure and glomerular blood flow. The former influence would result in diuresis; the latter in diminished urine; and it is known that each of these effects may be elicited by adrenalin if dosage be suitably chosen. It seems to me wholly probable that both types of action may be exerted by concentrations of adrenalin which exist at

different times in the arterial blood as the result of activity of the suprarenal glands.

Another aspect of the same problem concerns the action of dilator substances. It has long been known that substances which pass readily into the urine and which cause diuresis cause also dilatation of the renal bloodvessels. I refer to increased water content of the blood, to such salts as sodium chlorid, sodium sulphate, sodium bicarbonate, and to sugar, to urea, to caffein and its derivatives. It is at once obvious that any substance which dilates renal bloodvessels without simultaneously producing a fall in aortic pressure will thereby increase the rate of blood flow through the kidney. Such increased blood flow *per se* would be a diuretic factor, for the reason that the rate of renewal of contact of fluid from which filtrate is produced with the membranes through which the filtrate passes would be increased. But whether or not intraglomerular pressure will be increased by vascular dilatation of the kidney will depend upon the relative degree of action upon afferent vessels and upon efferent vessels or vessels distal to the glomerular tuft. The question is therefore pertinent whether such substances as I have mentioned possess the power of dilating the afferent vessels to a greater degree than the efferent vessels.

There were some *a priori* reasons for imagining that this might be the case. We have proved that between the afferent and the efferent arteriole the blood plasma is concentrated by loss of fluid which contains no protein. Consequently the colloid content of the plasma of the blood which is flowing through the efferent vessel is greater than that of the plasma of blood flowing through the afferent vessel; the question therefore arose whether the colloid concentration of fluid in which a vasodilator substance is dissolved may affect the intensity of its action. This suggestion, made four years ago,[24] has only recently been subjected to experimental test. Hamburger's modification of Ringer's solution was adopted as a suitable fluid with which to perfuse the vessels of the frog's kidney from a glass reservoir in the usual way. Four solutions were prepared for a single experiment, two containing as a colloid purified acacia in concentration of 3 per cent. Two other solutions were similarly prepared in which the colloid concentration was 6 per cent. Caffein in amount to make 0.1 per cent was added to one sample of the 3 per cent acacia, and to one sample of the 6 per cent acacia. The arrangement of perfusion reservoirs was such as to permit accurate comparison of the dilating action of 0.1 per cent caffein in 3 per cent acacia with that of 0.1 per cent caffein in 6 per cent acacia. Results were expressed in terms of rate of flow through the organ per minute, perfusion pressure being maintained constant. The result exceeded expectations. In every instance it was found that the dilator action of caffein in 6 per cent acacia is very markedly less than in 3 per cent acacia. Similar

results were obtained in experiments in which sodium nitrite and sodium chlorid were tested.

These results show that the peculiar arrangement of the glomerular capillaries in relation to the afferent and efferent arterioles is such that substances which dilate these arterioles produce greater dilatation of the afferent than of the efferent. Thus intraglomerular pressure is raised and increased filtration occurs. Since we know that renal vessels react very sensitively to dilator substances, we can see how it is that a slight increase in water, salt, urea content, etc., of the blood automatically produces such an alteration of these vessels as to provide conditions favorable for increased glomerular elimination and hence for ridding the blood of such excess.

While our first observations on the effect of minute doses of adrenalin on the size of the glomerular tuft were in progress, other features of the glomerular circulation became apparent, and it was soon evident that these might properly be looked upon as evidences of the fashion in which glomerular function is adjusted to bodily requirements.[25] Some preparations of the frog's kidney were encountered in which very few glomeruli were visible; in others many were to be seen. The visibility of the glomeruli was dependent upon the presence of blood corpuscles within their capillaries. We soon found that the number of visible glomeruli in a preparation in which it was small could be increased by many of the common means of increasing renal circulation, such as section of the sympathetic nerve supply, injection of salt solution, transfusion of blood, injection of salts, of sugar, of urea, etc. On the other hand, the number could be diminished by means which are known to produce constriction of renal vessels, such as stimulation of sympathetic, large doses of adrenalin, or of pituitary extract. These observations yielded proof that in the frog's kidney the fraction of the total glomerular equipment which receives blood and hence which functions at any one time is variable, and thus evidence is afforded in support of the conception that the degree of glomerular activity of the whole kidney is susceptible of adjustment by increase or decrease in the number of glomerular units which are active. This conception was very clearly stated sixty-five years ago by Hermann,[26] a colleague of Ludwig's, but, so far as I know, no definite experimental evidence in support of it has previously been advanced. It is well known that comparatively slight changes in the composition of the blood—changes which are hardly discoverable by chemical means—are capable of producing a diuretic response which seems disproportionately great. If we conceive that a renal vasodilator substance increases the rapidity of renewal of blood plasma in contact with glomerular surface, increases intraglomerular pressure by a greater degree of dilating action upon the afferent than upon the efferent vessel, and in addition causes an

actual increase in the number of glomerular units involved, we have the basis of an explanation of such apparent disproportionate effects. It will be recalled that the work of Gotch, Keith Lucas, Lodholz, and Adrian[27] showed that the intensity of response by muscle to stimulation of its motor nerve is dependent upon the number of fibers in the nerve which take part in the transmission of the impulse. It will be recalled that Krogh showed that the number of patent capillaries in a muscle varies with the physiologic state of the muscle.[28] Our observations show that the number of glomerular units which take part in renal activity may similarly vary to meet changing demand on the part of the organism for excretory function.

These observations on the frog's kidney will not be accepted as immediately transferable to the physiology of the mammalian or human kidney without question. Thus far it has not been possible successfully to subject the mammalian kidney to methods of direct observation. But in respect of variability of number of glomeruli involved in the function of the whole kidney at any one moment, indirect methods are available. Kanolkhar,[29] in London, injected hemoglobin solutions intravenously into animals, removed the kidney and in thick sections of the cortex counted the number of glomeruli which showed traces of hemoglobin and of those which did not, he came to the conclusion that events similar to those which we had described in the frog's kidney took place in the mammalian kidney. Dr. Hayman and Dr. Starr,[30] in our laboratory, have carried through a series of experiments similar to these in design. They used Nelson's method for estimating the number of glomeruli.[31] This consists in staining the glomerular tufts by passing a solution of Janus Green B through the renal vessels, dissecting the cortex away from the medulla, and counting the stained tufts in a small weighed section of the cortex. Knowing the weight of the whole cortex, the total glomerular count for the whole kidney is easily ascertainable. After convincing themselves of the reliability of the method, they found that the number of glomeruli in the two kidneys in a normal rabbit is approximately the same. Then the following procedure was adopted. From the anesthetized rabbit suitably prepared, one kidney was excised without hemorrhage, and laid aside for subsequent enumeration of the total number of glomeruli in it. The condition to be studied was then established in the animal, (that is, injection of diuretic, of adrenalin, and so forth) a solution of Janus Green B injected into the aorta above the remaining kidney, and within twenty seconds of the end of the injection this kidney was excised. Obviously the dye could reach only such glomeruli as were receiving blood at the time of injection and during succeeding seconds. Glomerular count of the intravitally stained kidney compared with the total glomerular count of the other showed the fraction of glomeruli which were

receiving blood during the presence of the dye in the circulation. A long series of experiments was made, the results of which are convincing. They showed that from 50 to 85 per cent of the total glomerular equipment of the rabbit receive blood under control conditions. If a diuretic, such as caffein or NaCl, was given from 95 to 100 per cent of glomeruli receive blood. If graded doses of adrenalin were given, or if vasoconstriction were produced by inhalation of CO_2, or if the splanchnic nerve were stimulated, the number of glomeruli receiving blood could be diminished at will to 40, 30, 20, 10 or 5 per cent of the total glomeruli present. These experiments appear to me to furnish adequate proof that the observations made on the frog are acceptable for the interpretation of events which take place in the mammalian organ.

Proceeding from the conception that mechanisms are at the disposal of the kidney, whereby a greater or smaller number of its glomerular units may be utilized in the filtration of fluid from the blood in accordance with the excretory requirements of the body, we may properly ask how it is that damage is avoided to those glomerular structures through which temporarily no blood is flowing? One of the oldest observations in the history of renal physiology is to the effect that interruption of the renal circulation for a short time (minutes) results in albuminuria when the interruption has ceased. If, then, during any prolonged period the kidney uses, let us say, only 60 per cent of its glomeruli, how is it that the other 40 per cent escapes the damage which could be expected to result from lack of circulation through them? The answer to this question begins in observations which were made immediately after we had discovered how to look at the glomerular circulation in the frog's kidney. It was seen that the flow of blood through the glomerular capillaries in many experiments was not continuous, but was irregularly intermittent. This intermittence was not synchronous with the heart beats, nor was it uniform or regular for individual glomeruli which could be simultaneously observed. This observation suggested the probability that while the total number of glomeruli of the kidney were not necessarily suffused with blood at any one moment, yet by individual variations of blood flow in individual glomeruli the total glomerular equipment might be suffused within a period short enough to prevent the damage which more prolonged anemia would entail; and this suggestion was adopted as an interpretation of the broader significance of the observed interruptions in glomerular flow.

But how this phenomenon of intermittence is produced was for a long time a complete mystery. It became clear that the intermittent cessations of blood flow through individual glomerular tufts were not due to constrictions of capillaries composing the tufts. It could be seen that intermittent flow included the arterioles leading to the tuft, and hence the glomerular cessations are in

reality arterial or arteriolar phenomena. Finally Langley's work[32] on the nervous control of the smaller arteries in the web of the frog's foot was encountered, and its bearing upon our problem recognized. He showed that when a nerve supplying a vascular area in the frog's web is stimulated repeatedly the resultant constrictions of the smaller arteries do not uniformly involve the same vessels; vessels which contract to one stimulus are not necessarily the same as those which responded to the preceding one. He made the suggestion that the physiologic condition of the muscle of the arteriole may so vary as a result of its contraction that at one time it may be refractory to a stimulus to which it responds at another. This led me to think that in the kidney the smallest arterioles might undergo alterations in their readiness to respond to constrictor influences and that such alterations might be responsible for the observed intermittence. In harmony with this thought was the observation that intermittence is most apt to be encountered in the frog if the upper part of the spinal cord has not been injured in the process of destroying the brain, the operation which we use to avoid the necessity of anesthesia. The upper part of the spinal cord in frogs contains a large share of the central nervous mechanism for controlling the caliber of the bloodvessels. It appeared, then, that it might be possible to produce artificially an intermittence of the glomerular circulation by subjecting the vessels of the kidney to a constant constrictor influence of a moderate grade of intensity. Three groups of experiments were made. In one the central end of the sciatic nerve was stimulated during observation of blood flow through a group of glomeruli; in another the ramus communicans from the fifth spinal nerve which contains vasoconstrictor fibers to the kidney was stimulated; and in the third a dilute solution of adrenalin was injected at an extremely slow but constant rate into the abdominal vein. In each experiment a group of glomeruli was closely watched before, during and after the period of stimulation. It became very clear that each of these three means was capable of inaugurating in a previously uniform glomerular circulation an intermittence precisely similar to that which we had previously seen occur spontaneously. And hence we have the basis for belief that when the bloodvessels of the kidney are subjected to a constant nervous or chemical constrictor stimulus the response exhibited by the vessels concerned is an intermittent one. We picture the process to occur as follows: It has been known since the time of Lister and Cohnhein that if a vascular area is rendered anemic by clamping its artery for a time, when blood is readmitted, the vessels are dilated as though their tonus had been diminished by the asphyxia to which they had been subjected. Some years ago I found that when the vessels of the heart or the vessels of the leg of a dog were perfused with fully oxygenated Ringer's solution the substitution of identical Ringer's solution containing no oxygen

caused them to dilate immediately.[33] We may therefore regard it as proved that lack of oxygen has a dilator influence upon arterial muscle. If, then, a small artery in the kidney is constricted as a result of a nervous or chemical influence so that no blood passes through it, the asphyxia of its muscle so induced leads to a progressive decrease in its power to continue reacting to that stimulus; so that eventually, assuming the stimulus to be moderate in degree, the muscle must relax, the artery opens and blood flow through it is resumed. When blood flow returns, and with it adequate nutrition of the muscle wall of the arteriole, this again becomes responsive to the constrictor stimulus and again the vessel may close. We may conceive such a process, involving many vessels, and hence many glomeruli, as capable of producing just such an intermittence as I have attempted to describe.

There is another fashion in which the surface of glomerular capillaries available for filtration is variable. The capillary pathway in the single tuft in the frog's kidney very often can be seen to consist of three primary branchings from the afferent vessel, each of which in turn undergoes a secondary branching. One frequently sees that the blood current entering a glomerulus flows largely into one of the three primary divisions and scantily into the other two. In some instances only one capillary channel will be seen in a tuft, but if any one of the various vasodilator influences which I have mentioned are introduced into the blood stream other capillary channels in this tuft may open and become visible by reason of the stream of corpuscles passing through. I have spoken of intermittence of the glomerular circulation, using this term to indicate the fact that blood often ceases to flow temporarily throughout the whole tuft; intermittences of individual capillaries within a single tuft have been plainly seen. In the most striking illustration of this fact which I have encountered the blood current through a tuft during the early minutes of observation was confined to one apparently dilated capillary. While I was watching the flow of blood through this a second capillary suddenly made its appearance, branching from the origin of the first; presently a third similarly appeared, and during the succeeding minutes of observation these two alternately opened and closed, while blood flow through the first remained steady and uninterrupted. When viewed by reflected light under varying circulatory conditions, remembering that the capillary pathway is discernible almost only by corpuscles passing through, the appearance of a single tuft may be so different at different times as to make it difficult to believe that it is a single structure which is under observation.

For a long time we were under the impression that these changes in capillaries within a single tuft were caused by changes in the caliber of the capillary presumably brought about as a result of nervous influence exerted upon it. One citation from the anatomic

literature can be advanced (Smirnow) indicating that nerve fibrils pass into the capsule of Bowman and are related to the capillaries enclosed within it; but when the changes which occur in the circulation within a single capillary of a glomerulus are more closely observed, using higher powers of the microscope, one fails to discover signs that the caliber of the capillary tube decreased during such interruptions as I have described. Into such a capillary a single corpuscle may be seen to enter. It passes slowly through and disappears, but during its passage it is not distorted as would necessarily be the case were the capillary narrowed, but on the contrary can be seen to rotate on its various axes and apparently to bump from side to side as though floating in transparent fluid flowing through a relatively wide tube. Observations of this sort have led to the view that alterations in the caliber of glomerular capillaries resulting from their own contractility are yet to be proved. Such events as those just described can be more satisfactorily accounted for by alterations in diameter of the openings from the afferent vessel into glomerular capillaries. We have suggested that these openings may have sphincter-like properties, may undergo rhythmic alterations in tonus and may be more sensitive to constrictor or dilator influence, nervous or otherwise, than is the capillary wall. Indeed, Dr. Schmidt made observations, and I have confirmed them,[34] which indicate that constrictions under the influence of adrenalin occur more effectively at branchings of the smaller arterioles in muscle than at intermediate points, and in the older literature are to be found descriptions of phenomena which accord well with this statement. In the very recent work of Landis on pressure within capillaries further evidence has been encountered which is in harmony with this statement.

Another mode of adjustment of glomerular filtration may be mentioned. It is obvious that the glomerular capillaries are in a peculiar situation in that they are enclosed by Bowman's capsule which forms a strong and highly elastic envelope. We know that fluid issues from these capillaries into the intracapsular space from which it flows into the tubule. We know that fluid in different capsules is subject to different degrees of pressure which depend upon the pressure within the glomerular capillaries, upon ease of passage of fluid through the walls of these, and upon ease of exit of fluid down the tubule. Evidence of such varying intracapsular pressures can be obtained by simple inspection of a kidney which is forming urine. The degree of distention of different capsules which come within the range of one's vision is highly different, and if uniform pressure is exerted upon the surface of a kidney by means of a fragment of coverslip, it is seen that the flow of blood may stop completely in the capillaries of one tuft, while it is vigorously maintained in those of another. Regarding the glomerular process as one of filtration, it is obvious that filtration pressure is the differ-

ence between the pressure inside the capillaries and the pressure outside. The more rapid the accumulation of the outside pressure, and the higher the point which it attains, the more rapidly must an impediment to filtration accumulate. Such an accumulating impediment must act as an automatic brake to the process. If one perfuses the frog's kidney with oxygenated salt solution to which a trace of India ink has been added to render the capillary tufts more easily visible, and if the pressure under which the perfusion fluid is flowing through the kidney is suddenly raised, many visible tufts undergo obvious increase in size. Some do not, but if after previous laceration of a few of the capsules of the visible glomeruli a similar increase in pressure is induced, then it is found that the increase in size of the capillary tuft in these is decidedly greater than before. In other words, the capsule of Bowman, which serves as a chamber for collecting the glomerular filtrate and transmitting it to the tubule, is also a protection to the glomerular capillaries enclosed in it, and prevents damage to these capillaries which might result from excessive capillary pressure; by the tension which it is capable of exerting over the fluid which is in it, it can slow down the filtration process. We are as yet ignorant of the pressures which exist in the glomerular capillaries and within the capsular space. The subject is one upon which Dr. Hayman is at present engaged, and the prospect is that we shall shortly have quantitative data by which to measure the correctness of these statements.

In review of the information which I have been able to present which bears on the question of glomerular regulation, it may be said that evidence now exists upon which to base belief that glomerular pressure and hence glomerular filtration is regulated not only by the gross circulatory events which have long been recognized, such as alterations in the arterial pressure, in the venous pressure and in the gross change of the renal vessels in relation to these, but also by fine adjustments of the caliber of the afferent and of the efferent vessel in relation to each other. The mode of adjustment is such as automatically to provide conditions suited to rid the blood of excess of any substances which dilate the renal arterioles and which pass through the glomerular membranes. The more important normal urinary constituents very certainly possess these properties. Evidence has been presented in support of the belief that the action of adrenalin includes constriction of the efferent vessel as well as of the afferent. The proved identity of the vascular actions of adrenalin with the effects of sympathetic nerve stimulation permits the results obtained with adrenalin to be applied to problems of nervous control of these vessels. The suggestion may be made that the normal state of tone of these minute arterioles, sustained by the tonic action of the sympathetic nerves and of circulating adrenalin is such as to maintain intraglomerular pres-

sure by slightly greater constriction of efferent vessel than of afferent, whereas an increased degree of vasoconstriction must diminish intraglomerular pressure by closing of the afferent vessel.

Glomerular regulation is also secured by changes in the number of glomerular tufts and of capillaries in the same tuft through which blood flows at any one time. This is equivalent to saying that the extent of endothelial surface available for filtration is variable, being increased by influences which dilate vessels and decreased by influences which constrict. Damage to the kidney by prolonged anemia of any of its parts is avoided by the provision of intermittence and this in turn is, we think, dependent upon the action of constrictor influences and the antagonistic dilator action of anemia which results from these.

Extracapillary intracapsular pressure which develops because of the elasticity of the capsule of Bowman, may act as an automatic brake upon the filtration process and at the same time is capable of protecting glomerular capillaries against undue distention from excessive intracapillary pressure.

We have described the process of filtration in the glomerulus as one not adapted to the interests of the organism as a whole, because it indiscriminately eliminates from the blood substances which the body should retain as well as those of which it should be rid. The tubule supplies the correction to this lack. But in the arrangements which have been developed for the circulatory control of the glomerular process we must see evidence of a very high degree of adaptation to the bodily welfare.

I have not touched upon the problem of permeability of glomerular membranes. I am convinced that variations in it occur and will eventually be demonstrated; but the direct experiment which compels belief has not been made.

Before closing, I wish to mention very briefly a series of experiments which may serve to relate some of the observations I have been describing to the practical problem of albuminuria. Four years ago it was suggested that if the period of intermittence of glomerular blood flow should be slightly lengthened an albuminurina might be anticipated to result.[35] The anticipation was based on the knowledge that temporary closure of the renal artery is followed by albuminuria and upon the evidence provided by Nussbaum that this is glomerular in origin.[36] Experiments were designed to test this thought and Dr. Starr has carried them out.[37] Normal healthy rabbits, given an intravenous injection of adrenalin in such amount and fashion that its action is maintained for several minutes, subsequently show transient albuminuria. Healthy cats, subjected to insults which they resent and which excite them to fear or rage, subsequently eliminate albumin. When the question was studied in anesthetized dogs under controllable conditions it was found that the course and degree of albuminuria which could

be produced by vasoconstrictor influences, such as adrenalin, stimulation of the splanchnic nerve, inhalation of CO_2, and so forth, was strictly analogous to that which could be produced by temporary partial obstruction of the renal artery. In exceptional experiments no renal vasoconstriction was produced by these means, and in these albuminuria did not occur; thus showing that the albuminuria was dependent upon the vasoconstriction and was not the result of direct action of the agents tried upon the glomerular membranes. Histological study showed no abnormalities of structure in these kidneys. Similar results have been obtained in man in a study by Dr. Grier Miller, now in progress in the University Hospital, of the effects of ephedrin—a drug of Chinese origin recently studied by Dr. Schmidt and K. K. Chen, in Peking, samples of which have been supplied to us by Dr. Chen. Their work showed that ephedrin causes vasoconstriction similar to but more lasting than that of adrenalin. In the cases studied by Dr. Miller tests made by Dr. Starr for albumin in the urine were positive in those cases in which distinct rise in blood pressure occurred; negative in those in which it did not. Maximum albumin elimination did not coincide with maximum height of blood pressure, but followed it.

These results show how renal vasoconstriction can lead to albuminuria and how a diuretic which opens up glomerular vessels which have previously been closed may appear to be a damaging agent upon renal structures, whereas in reality the damage of which the eliminated albumin is evidence was the result of the vasoconstriction which the diuretic abolished.

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STUDIES IN HUMAN CONSTITUTION.

III. Physical Types in Relation to the Toxemias of Pregnancy.

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NEW YORK.

For some time past at the Sloane Maternity Hospital, there has been a growing belief that the women who developed idiopathic hypertension during the course of pregnancy were of a morphological type which could be recognized. Less marked, but still recognizable, characteristics could be noted in toxemic cases in which nephritis was the outstanding feature. At the request of Drs. Studdiford and Herrick,[1] the Constitution Clinic of the Presbyterian Hospital undertook to make anthropometric studies of a series of cases which they selected. No attempt was made to reclassify the toxemias of pregnancy, and no existing classification was used rigidly as a basis for their selection of cases.

As is well known, a variety of conditions have been described under the head of the toxemias of pregnancy. There are numerous classifications, such as those of Kosmak,[2] Schiotz,[3] Cheney,[4] Kellogg[5] and others. These writers recognize besides the acute pernicious vomiting type and the acute yellow atrophy of the liver, in general two or three less fulminating forms in which high blood pressure or more or less severe nephritis appear either as the dominant symptom or in various combinations. The cases selected by Dr. Studdiford and Dr. Herrick included, so far as possible, examples either of idiopathic hypertension or nephritis. There were, of course, several individuals in whom both conditions existed. But when this was true the patient was classified according to the preponderance of one or the other. Because of the fact that the white race alone had figured in our previous studies, it seemed best at first to exclude negresses from the investigation. But the black race formed so

large a part of the total available material that it was finally decided to make comparative studies on these people also. Actually this turned out to be a most fortunate decision, for, as will be shown later, it provided a check on the method which had neither been sought nor expected.

The technic of measurement and the method of presenting the data in this study are essentially similar to those described in the author's book on *Human Constitution*. The material consisted of 117 cases, distributed as follows between the two races and the two pathological conditions:

White, hypertension	42 cases
White, nephritis	22 cases
Black, hypertension	25 cases
Black, nephritis	10 cases

It had been the impression at Sloane that the women with idiopathic hypertension were large, rather heavy-faced individuals, who often displayed hair distributions which suggested virilism. Indeed, with a proper academic restraint, they had been referred to as "pituitary types." Those patients whose predominant ailment was nephritis were not so well defined in character, but seemed to be in general smaller, thinner and less well developed.

For the satisfaction of the more critical students of this problem, it would be desirable to publish all the original numerical data gathered in the course of this investigation. But to present all the figures and tables in an article of this scope is impossible. They will be made available later however, in a larger monograph on the subject of hypertension and nephritis. For the present four figures are presented which show first of all, certain classical racial differences between the whites and blacks, and second, certain differences in bony structure between the two disease groups. The curves make apparent an interweaving of racial and disease group characters. From a technical standpoint these results are interesting and important because the same technic which correctly demonstrates the well-known anthropometric differences between the white and black races is applied to and shows equally great differences between the two disease groups.

In Fig. 1 appear in the form of cumulative percentage curves (Galton) differences in the radius length. Without entering upon an elaborate discussion of the structure of these curves, it may be said that displacements of the curves toward the right indicate greater lengths of radius. It will be seen that the difference between the races in respect of radius length is clearly shown by the grouping of the solid and broken line curves. Furthermore, it is apparent that the cross-hatched curve representing hypertension is in each instance on the long side of the uncross-hatched curve. These relationships reflect not only the accepted fact that the negro radius is longer than that of the white race, but also that in both

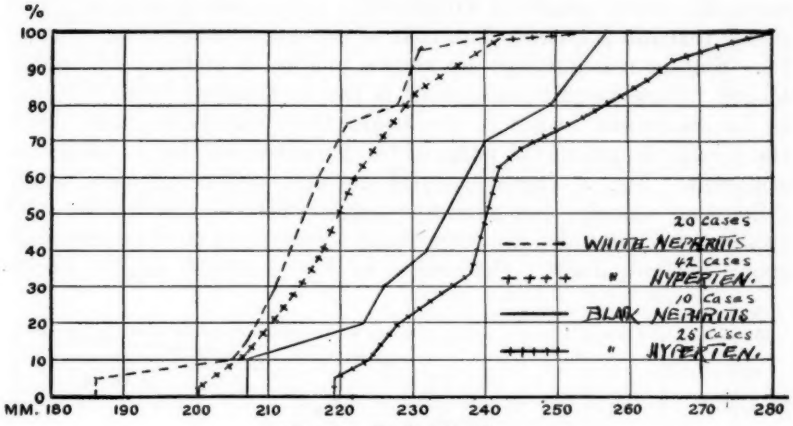

FIG. 1.—Radius length.

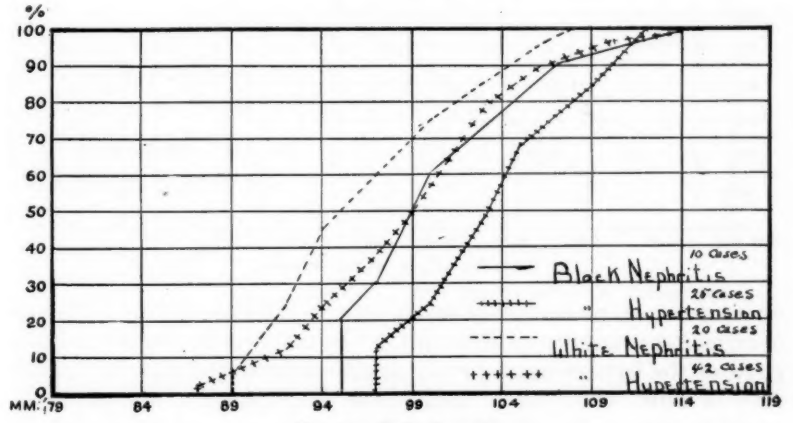

FIG. 2.—Palm length.

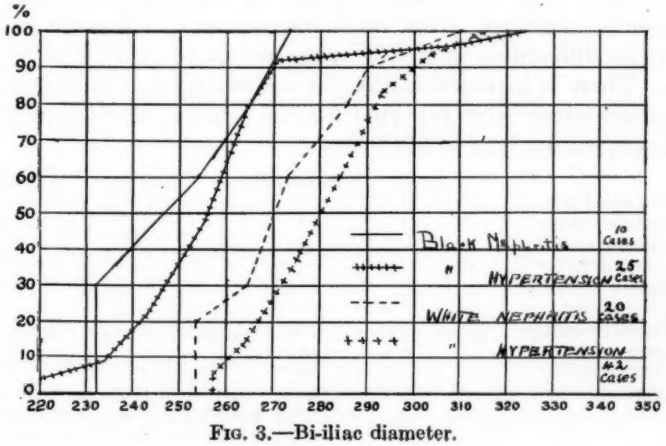

FIG. 3.—Bi-iliac diameter.

races the radius length of women with hypertension form of pregnancy toxemia is greater than that of women suffering from nephritis. Similar relationships are shown in Figs. 2 and 3. The palm length, whose largest component is the metacarpal bones, is seen to be somewhat longer in the negro than the white race. But the greater length of the palm of the hypertension cases is likewise apparent. Fig. 3 illustrates still another well-recognized racial difference; namely, the narrower pelvis width of the blacks. In this measurement also the larger bony structure of the hypertension group declares itself. The curves in Fig. 4, which express chest

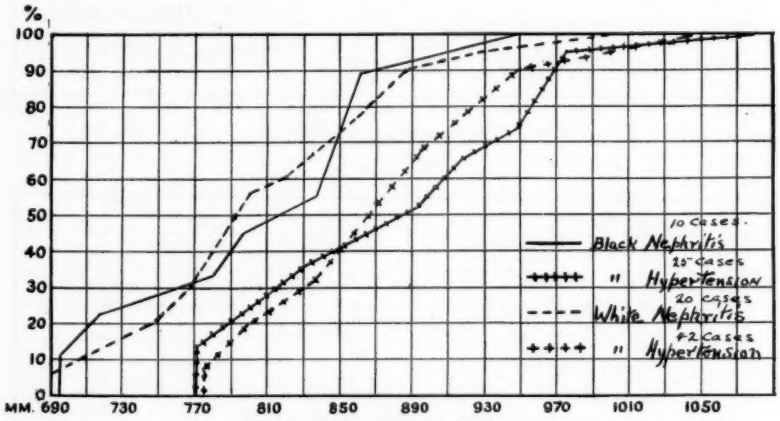

FIG. 4.—Chest circumference.

circumference, present a situation wherein disease group difference overshadows race group differences. In this case the larger thoracic girth of the hypertension people again confirms the general impression of bulk which these individuals had given. Similar graphs could be shown for all the other measurements and indices of the entire body, but space and expense of reproduction make this impossible. Instead, a list of characters and indices is given in which the differences in size or value are simply indicated by plus signs. There is included in this list a column for comparison with the values which were reported for the original series of nephritis and hypertension.[6] The list follows:

	Hypertension.	Nephritis.	Previous.
A—Head and Face:			
Cephalic length	+	−	=
Cephalic breadth	○	○	=
Facial diameter	+	−	=
Bigonial diameter	++	+	+
Facial height	+	−	−
Nasion prosthion	±	−	=
Nasal height	±	−	=
Nasal breadth	±	−	=
Id. ment.	++	−	=

(This measurement in white hypertension females is equal to that of male gastric ulcer.)

	Hypertension.	Nephritis.	Previous.
Mandible length	++	−	−
Asc. ram. length	+	−	−
Hor. ram. length	++	−	=
Gonial angle	+	−	−
Interpupillary space	+	−	−
Palpebral length	+	−	=
Palpebral breadth	+	−	=
	(Has this wide slit relation to hyperthyroidism?)		
B—Extremities and Linear Segments:			
Finger length	+	−	=
Hand length	++	−	=
Palm length	++	−	=
	(White nephritis group of origin G. B. group.)		
Span	+	−	=
Vertex (standing height)	+	−	=
Neck height	O	O	=
	(The nephritis-hypertension group original series had short necks.)		
Sternum length	+	−	=
SSN—AIS	±	−	=
XU-UP	O	O	Hyperten.-neph. group.
Humerus	+	−	−
Radius	+	−	=
Femur	+	−	=
Tibia	+	−	=
Thor. lat. diam.	+	−	=
Trunk	+	−	=
Upper extremities	+	−	=
Lower extremities	+	−	=
Subcostal angle	−	+	=
Chest circumference	+ (both races)	−	=
Thor. A. P. diam.	+	−	+
	(but hypertension is flatter than flattest of original series.)		
Bi-iliac diam.	+	−	=
Bi-acromial diam.	+	−	=
Neck circumference	+	−	−
Weight	+	−	−
Facial index	+ (longer and narrower)	−	=
Upper facial index	O	O	=
Nasal index	±	−	=
Palpebral index	Reflects wide fissures.		
Bi-acromial Stat. I	−	±	=
Int.-pupillary space nas. pros. I	O white	± O	
	(reflects wider fac. diam. of hypertension, int.-pupillary space being.)		
Hand I.	−	±	
Thor. L. D. Ch. L.	+	−	
Bi-acromial Stat. I.	−	+	
Chest circ. Stat. I.	±	−	
Thor. L. D. Ch. L. I.	+	−	+
Ponderal index	+	−	

Thus, all the measurements about the head and face show that the hypertension group have larger and heavier skulls and mandibles than the nephritis group. Furthermore in all linear segments, and particularly in the long bones, hands and fingers, greater length

is found among those with hypertension. The same circumstance is true for the girth of the chest. Now, while these findings satisfactorily support the observations of Doctors Studdiford and Herrick, they assume greater interest when considered in the light of our knowledge of acromegaly. Keith[7] has pointed out that the increase in bony growth in this disease follows definite and constant lines, though there may be more or less variation in its extent. In addition, he makes it clear that these enlargements take place exactly along the path of normal growth. Especially interesting are his demonstrations of the enlargements of the skull and mandible. For example, not only is the cephalic length increased in acromegaly because of the great frontal bosses and the growth of the posterior occipital protuberance, but the mandible develops added length in both ascending and horizontal ramii with a widening especially of the latter. This last increment results in a greater value for the inferior dental-menton distance. Now it is particularly interesting to observe that our measurements of the skulls and mandibles of the hypertension group of pregnancy toxemias show definite increases along precisely the same lines as those described by Keith as characteristic of acromegaly. Furthermore, the greater length of all linear segments, chiefly of the long bones, are, like the acromegaloid characters of the face, indications of a state which when exaggerated has been termed gigantism. Cushing[8] and others have pointed out that when the pituitary gland is overactive or unrestrained by other influences, before epiphyseal closure, gigantism results. More recently Evans[9] has shown the powerful growth-stimulating qualities which lie in the anterior lobe of the gland. There are, moreover, certain other remarkable physiological phenomena which are interesting in this connection. For example, that there is a definite checking influence which the gonads exert upon the growth-stimulating qualities of the pituitary is well recognized. Tandler and Grosz, in addition, have had the opportunity of studying the pituitary gland in castrate Skopsi. The gland was found by these observers to be considerably increased in size in these cases. During pregnancy also there are hypertrophic changes in the gland. These may be accompanied, as described by Cushing,[10] by indications of increased activity in one or more of the various fields wherein the pituitary gland functions. As the gland alternates under the recurring stimulus of pregnancy between hypertrophic change and involution, unusual opportunity is provided for distortions of function. For, as Cushing says, "It is readily foreseen, therefore, that ultrafunctional transitions with some manner of secretory perversion may be easily acquired . . . . and the transitory clinical manifestations of glandular overactivity already mentioned may persist or even increase after the termination of the pregnancy." Obviously then in the course of pregnancy one may expect not only hyperplasia but hyperactivity of the pitui-

tary gland. And it must not be forgotten that among its many qualities, it possesses a powerful pressor substance. Not only in pregnancy, however, but following castration and its physiological analogue, the menopause, there is hypertrophy with overactivity of the pituitary. The hypertensions of women at this stage of life are common enough.

It must not be inferred from the foregoing discussion of the disturbed physiology of the pituitary gland, that its increased activity in pregnancy is here being held responsible for the existing enlargements of bony parts disclosed by our measurements. The acromegaloid and gigantoid skeletons found in the Sloane cases simply bespeak the end result of a vigorous pituitary influence which acted much earlier during the growth period.

But the suggestion is advanced that such a vigorous gland, whose witness for high functional efficiency is the presence of acromegaloid and gigantoid insignia, may be driven by the conditions of pregnancy to far greater potency of action than an initially less powerful organ. Thus it would appear that the possession of a perhaps large and surely very active pituitary gland, which had assisted in the production of a massive frame, may actually hold a menace for the pregnant woman.

While it is not the purpose of this paper to enter upon a discussion of the mechanism of the nephritides and hypertensions which are not associated with pregnancy, yet attention must be called to the striking similarity of the measurements and indices here reported to those presented for that group in the author's book on *Human Constitution*. In that communication the statement was made that the women of the hypertension-nephritis race were larger women in comparison with women of all other disease races. At first the combining of hypertension cases and nephritis cases in one group was undertaken with considerable hesitation. But it is rather significant that when the figures from the two types of pregnancy toxemia were analyzed, it was found that the nephritis group was composed of individuals who appeared simply to be slightly smaller reproductions of the hypertension-type design.

Conclusions. 1. The original contention of the observers at Sloane, that the hypertension people were larger, heavier, more masculine types than the nephritis people, is borne out by anthropometric studies.

2. The changes or increases in the bony skeleton are precisely along the line of increase found in acromegaly or gigantism.

3. Women of a certain constitutional type, whose skulls, mandibles and skeletons display the insignia of a previously increased activity of the pituitary gland, may under the specific stimulus of pregnancy develop hypertension or nephritis, either transient or permanent.

4. The closeness of the two groups in morphological characters

and their approximation to the combined hypertension-nephritis series suggest that idiopathic hypertension and nephritis are different expressions of one and the same disease.

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OBSERVATIONS ON THE DIAGNOSIS OF SUBPHRENIC ABSCESS.

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Although a considerable literature exists on the subject of subphrenic abscess, and although the condition has been capable of clinical recognition since Leyden,[1] in 1880, described the process, its symptoms and its signs, still the diagnosis of subphrenic abscess is often obscure and almost always difficult until such a time as the condition has become well established. Therefore, it has seemed worth while to discuss this interesting disease, and to cite certain matters germane to its diagnosis which have come to my attention in the observation of a series of cases.

Previous to Leyden's description, subphrenic abscess was of pathologic interest only. Leyden's study first made it possible for the condition to be recognized clinically. Since then the studies of Maydl,[2] Piquand,[3] Barnard,[4] Elsberg,[5] Lockwood[6] and others have contributed much to the understanding of this always insidious and often serious condition. Many other lesser studies and case reports are to be found in the literature; but even yet subphrenic abscess frequently remains unrecognized for long periods of time. The reasons for this will be apparent in the course of the discussion.

Anatomy. In order to understand the formation of subphrenic abscess it is necessary to be conversant with the relations of the diaphragm to the structures and organs below it. The space below

the diaphragm may be divided anatomically into six areas: The right and left extraperitoneal spaces, the right anterior intraperitoneal space, the right posterior intraperitoneal space, the left anterior intraperitoneal space, and the left posterior intraperitoneal space.

The right extraperitoneal space is that area uncovered by peritoneum between the folds of the coronary ligaments as they are reflected onto the diaphragm. The left extraperitoneal space lies above the upper pole of the left kidney, where the peritoneum is reflected onto the diaphragm.

The right anterior intraperitoneal space has the diaphragm and the liver below it. To the right is the falciform ligament; behind, the space extends to the right lateral ligament of the liver. This area connects with the right posterior intraperitoneal space and also with the lumbar fossa which lies between the ascending colon and the loin, the socalled pericolic groove, which gives a direct connection between this space and the region of the cecum and of the pelvis. Because of this connection, abscess is most common in this space, and it may be considered as the only true subphrenic space on the right side.

The right posterior intraperitoneal space is bounded to the right by the abdominal wall; in front by the liver and gall bladder; posteriorly, by the upper pole of the right kidney and the crus of the diaphragm. It is connected with the left intraperitoneal space, which is in reality the lesser peritoneal cavity, by the foramen of Winslow. Infection in the lower abdomen may gain access to this space through the lumbar fossa; on the other hand an infection in the lesser peritoneal cavity may enter this space through the foramen of Winslow.

The left anterior intraperitoneal space is surrounded by the falciform ligament, the stomach and the spleen, with the diaphragm above, and extends as far backward as the left lateral ligament of the liver. The floor of this space is formed by the tail of the pancreas and by the left kidney. While there is no direct connection between them, this space is only lightly shut off from the right posterior intraperitoneal space, and it is connected with the lower abdomen by the left lumbar fossa.

The left posterior intraperitoneal space is analogous to the lesser peritoneal cavity. It is important to remember that part of the boundary of this space is formed by the posterior wall of the stomach and of the duodenum. As has been said before, there is free connection between this cavity and the right posterior intraperitoneal space through the foramen of Winslow. These anatomic connections and surroundings indicate how readily infection situated in the abdominal or retroperitoneal viscera may be carried to one of the subphrenic spaces, and thence by these intimate connections to other regions below the diaphragm.

Etiology. Most subphrenic abscesses are due to infection following acute inflammation or perforation of one of the abdominal viscera, either before or after surgical intervention. A few occur from direct extension from an abscess adjacent to one of the subphrenic spaces, such as a perinephric abscess. More rarely subphrenic abscess is caused by infection through the blood stream from a more distant focus. Lee[7] has reported 4 cases which were apparently spontaneous in origin. The infection may originate in the thorax and spread downward to the subphrenic spaces, but this is uncommon.

By far the most common sources of subphrenic abscesses are: (1) Appendicitis, (2) ruptured gastric ulcer and (3) ruptured duodenal ulcer. Statistics vary as to which of these conditions is the most frequent cause, but it is generally believed to be the appendix. Abscess of the liver, either amebic, from an infected hydatid cyst, or from an ordinary pus infection, gall bladder disease, abscesses of kidney, spleen or pancreas, have all been described as etiologic factors. Right subphrenic abscesses usually follow appendicitis, liver or gall bladder disease, or are of duodenal origin; whereas, abscesses under the left diaphragm usually follow disease in the stomach, pancreas or spleen. It is interesting to note, however, how many left-sided subphrenic abscesses follow disease of the appendix.

The method by which infection reaches the subphrenic spaces is: (*a*) By direct extension from a localized or general peritonitis; (*b*) by the blood stream through the portal vein, or through the arteries, as in general infection; (*c*) by the lymphatics. The lymphatic connection between the subphrenic spaces and the abdominal viscera is threefold:

1. The retroperitoneal cellular tissue.

2. From around the deep epigastric artery to the falciform ligament, which is in close association with the lymphatics of the appendix and colon.

3. The subphrenic lymph spaces which pass through the diaphragm connecting with the subpleural plexus of lymphatics. While the march of the infection in these cases is usually from the subphrenic space upward through the diaphragm, it sometimes occurs from the pleural cavity downward.

The subphrenic abscess may contain pus alone, which is usually foul, and not infrequently contains gas as well as pus. It is believed that the gas is almost always due to bacterial action. Rarely air may enter the subphrenic space through a permanent fistula connecting it with a hollow viscus.

Symptoms and Signs. In most cases a history suggesting a gastric or duodenal ulcer, gall bladder disease or appendicitis can be obtained. The actual onset of the subphrenic abscess may be either acute or insidious. It is usually insidious following some

acute inflammatory disease of the abdominal organs or the rupture of a hollow viscus. More commonly it follows an operation for some such condition. It has been estimated that almost 1 per cent of appendicitis, which has caused abscess or rupture of the organ, is complicated by abscess beneath the diaphragm.

The course of the condition in these cases is usually as follows: After the operation for the relief of the acute condition, convalescence starts normally, then after a longer or shorter period of time the temperature begins to rise again, and it is evident that all is not well. The temperature rises daily and is of a septic type, varying several degrees in the twenty-four hours. The pulse becomes rapid in proportion to the fever, but the respirations are not usually increased in rate. This fact may be of some importance in the diagnosis. The patient complains of pain, the location of which will depend to some extent on the location of the abscess. If the abscess be in the left or right anterior intraperitoneal spaces, the pain will be referred to the upper abdomen and also will be referred along the distribution of the phrenic nerve, owing to the irritation of the diaphragm. This pain will manifest itself along the upper border of the trapezius muscle, or in the side of the neck. If the abscess be in one or the other of the posterior spaces the pain may be referred to the loin or to the region of the scapula. Hiccough due to diaphragmatic irritation is said to occur in about 50 per cent of the cases, though in the cases to be reported hiccough did not occur in a single instance. Vomiting is not uncommon. As the condition advances the patient develops chills and sweats, and presents the characteristic appearance of an individual suffering from a retained septic process. Emaciation is usually rapid and marked. As the abscess grows larger the condition grows worse, and after a period of time, if proper treatment is not instituted, the infection spreads upward through the diaphragm, causing involvement of the pleural sac, which leads to the effusion of fluid and later to empyema, to infiltration of the lung or to abscess of the lung. When this has occurred, respiratory symptoms, such as cough, dyspnea and pleural pain, will be added to those which already exist. If no treatment is instituted the abscess may rupture through the lung, into the stomach, or into the intestine, and may heal spontaneously.

The physical signs will depend to a certain extent on the location of the abscess, the duration of the process and on the presence or absence of gas within it.

The motion of the chest on the affected side will be limited, and the more the diaphragm encroaches on the chest cavity, the more marked will be the limitation of motion. In late cases where there is secondary involvement of the pleural cavity with effusion, limitation of motion will be great. Theoretically, the movements of the costal margins should be of help in the diagnosis of subphrenic

abscess, but this sign cannot be depended upon in all the cases. Hoover[8] has shown that when the diaphragm is displaced upward it is at a mechanical disadvantage in exerting its pull on the costal margin, and, therefore, under these conditions the costal margins will move away from the midline to a greater degree than normal. In the 6 cases of subphrenic abscess which I have observed, movements of the costal margin were consistent with a high position of the diaphragm in but 3 of them. In 1 of these cases the abscess was on the left side; in the other 2 the abscess was presumably in the right extraperitoneal space. In the other 3 cases the costal margin did not move at all. In these cases the abscess was on the right side, and presumably involved the right intraperitoneal space. In 1 of these cases autopsy showed the liver so firmly adherent to the costal margin as to make any movement of the costal margin impossible. It is interesting to note that the right anterior intraperitoneal space is the most common spot for subphrenic abscess to begin, and also that the liver is always adherent to the inner side of the costal margin when infection is set up in this space.[4,6] For this reason the absence of the characteristic action of the costal margin cannot be taken as evidence against a subphrenic abscess. When the costal margin is found to flare more than normally the sign is of distinct diagnostic importance.

There may be localized bulging, depending upon the position of the abscess. The epigastrium may bulge, and the bulging may increase or decrease with the change of position of the patient. This change is due to the action of gravity upon the fluid within the cavity.

Palpation may reveal deep tenderness over the upper abdomen, or in the loin.

Percussion will show dulness over the chest on the affected side; sometimes the dulness is but slight. Later it will become marked and extensive. If there be gas within the abscess there will be an area of tympany which shifts with change of position. Below this area of tympany will be found an area of flatness corresponding with the fluid level within the abscess. In one of my cases dulness in the lower right chest gave way to tympany on change of position. Over the chest on the affected side the breath sounds are usually diminished, as is the vocal and tactile fremitus. Later, as the process extends upward into the lung or pleura, the breath sounds may be characteristic of fluid in the chest, and if the lung itself is involved, rales and bronchial breathing may be heard. The presence of a succussion splash heard over the suspected area is of the utmost importance, as it can mean but one thing—the presence of air and fluid. In 1 of my cases a left-sided abscess, a succussion sound synchronous with the heart beat was heard just below the heart. On fluoroscopic examination, the fluid could be seen to be rhythmically agitated by each heart beat. As far as I

can find out, from a review of the literature, this is the first time that this interesting auscultatory sign has been noted in left-sided subphrenic abscess. A friction rub over the lower chest is not uncommon, and usually means that extension into the pleural cavity has begun.

The heart is rarely, if ever, displaced either to the right or to the left—a point which is of importance in differentiating the condition from effusion into the chest cavity. In large left-sided abscesses the heart is displaced upward.

The position of the liver should be noted. Theoretically the liver should be displaced downward, especially when the abscess is on the right side. But, as has already been pointed out, in right-sided abscesses the liver is frequently adherent to the lower costal margin, and, therefore, cannot be displaced downward. The absence of a low position of the liver, therefore, cannot be taken as evidence against a subphrenic abscess.

When a subphrenic abscess is suspected, examination with the Roentgen ray should always be made. When the patient's condition allows, both fluoroscopic examination and films should be made, and to be entirely successful examination should be made with the patient in the erect posture. If there be a subphrenic abscess the diaphragm will be found to be in a higher position than normal, and often acutely arched. There may be only slight upward displacement in early cases, but as the process increases the diaphragm may be found as high as the level of the third rib. The fluoroscope reveals always a loss of motion of the diaphragm on the affected side, a finding which is of the utmost importance in differential diagnosis.

Case Reports. The following cases have been observed during the past four years:

CASE I.—J. B., a man, aged twenty-eight years, was admitted to St. Alexis' Hospital with an acute appendicitis. At operation a gangrenous retrocecal appendix with a beginning peritonitis was found. After the operation the patient made good progress for a period of four weeks, after which the temperature began to rise. A week later the temperature was 103° C.; pulse, 150; respirations but 20. The patient was very sick, and dulness and rales were found at the base of the left lung. The signs in left chest increased steadily, and the patient grew slowly worse. Four weeks after the onset of the fever the condition was as follows: The patient was emaciated and very ill; the temperature was 103°; pulse, 150; respirations, 30. The upper left chest lagged. The left costal margin flared more than the right. From the sixth rib in the axilla, and at the same level in the back, there was marked dulness, with absent vocal and tactile fremitus, and distant breath sounds and numerous moist rales. Over the ensiform cartilage, and just below the apex of the heart, there was a metallic tinkling succussion sound synchronous with the heart beat. There was also a marked succussion splash heard over the left axilla. The fluoroscopic examination showed the left diaphragm 3 or 4 inches higher than normal, and acutely arched. There was no excursion of the diaphragm; a large collection of gas was seen below the diaphragm, and below

this a fluid level which was thrown into waves by the heart's action and when the patient was shaken. The costophrenic angle was hazy, and there was evidence of infiltration in the base of the left lung.

Operation revealed a large collection of pus below the left diaphragm, which was drained. The patient died two days after the operation.

Comment. The points of interest in this case were the occurrence of of subphrenic abscess on the left side following an appendicitis and the presence of the very unusual succussion sound when the heart's action agitated the fluid below the diaphragm. In this case the movement of the costal margin pointed to a high position of the diaphragm.

CASE II.—F. P., a man, aged thirty-four years, was admitted to St. Alexis' Hospital. Ten weeks before admission he had sudden sharp epigastric pain. The pain was relieved by vomiting and by the ingestion of sodium bicarbonate. Since the onset the pain has been more or less constant, recurring at least once daily. On admission the patient complained chiefly of loss of weight and strength. Physical examination showed a sallow, emaciated individual; temperature, 100°; pulse, 80; respirations, 20. The movements of the right chest were limited. The right costal margin moved not at all. Percussion showed flatness from the angle of the scapula downward, from the sixth rib in the axilla and from the fourth rib in the midclavicular line. The dulness shifted with change of position, and the area in front became tympanitic when the patient was lying down. The breath sounds were very distant. A few crackling rales were heard at the base of the right lung. Succussion sound was present. The liver was not displaced downward.

Roentgen ray examination showed the right diaphragm at the fourth rib. Excursion was absent. The costophrenic angle was obliterated. Below the diaphragm was a clear space, below which there was a fluid level which was seen to splash when the patient was shaken. There was evidence of infiltration in the base of the right lung.

A diagnosis of right subphrenic abscess resulting from a gastric or a duodenal ulcer was made. The patient refused operation. However, he returned to the hospital a month later, at which time the abscess was opened and drained. The patient made a complete recovery.

Comment. It is interesting to note that in this case the onset was insidious; also that the costal margin moved not at all and that the liver was not pushed down. It is fair to suppose that in this case the liver was firmly adherent to the costal margin, as the infection involved the right anterior intraperitoneal space, spreading thence from the lesser peritoneal cavity.

CASE III.—M. F., a girl, aged thirteen years, was admitted to St. Alexis' Hospital with a ruptured gangrenous appendix, and was operated on immediately. Her progress was satisfactory until three weeks after the operation, when the temperature rose to 102° and continued to show a daily rise from then on. Four weeks after admission the condition was as follows: The motion of the right chest was greatly limited; the right costal margin moved not at all; percussion showed dullness from the third rib in the midclavicular line which extended to the axilla and back. The breath sounds were very distant. The vocal and tactile fremitus were much diminished. A small pleural friction rub was heard just below the right nipple; there was no succussion splash. The liver was not displaced downward. Roentgen ray examination showed the right diaphragm at the upper level of the fourth rib; the excursion was absent; the costophrenic angle was hazy, but the lung was clear (Fig. 1). A diagnosis of subphrenic

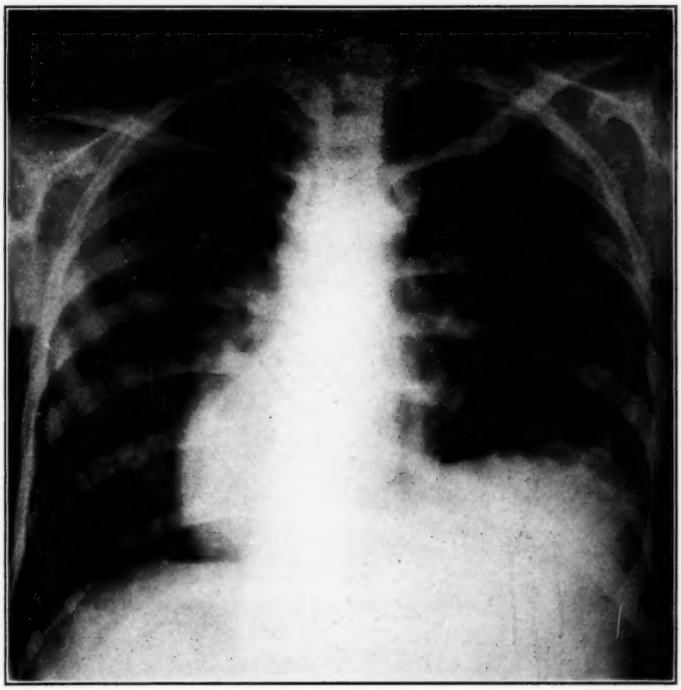

FIG. 1

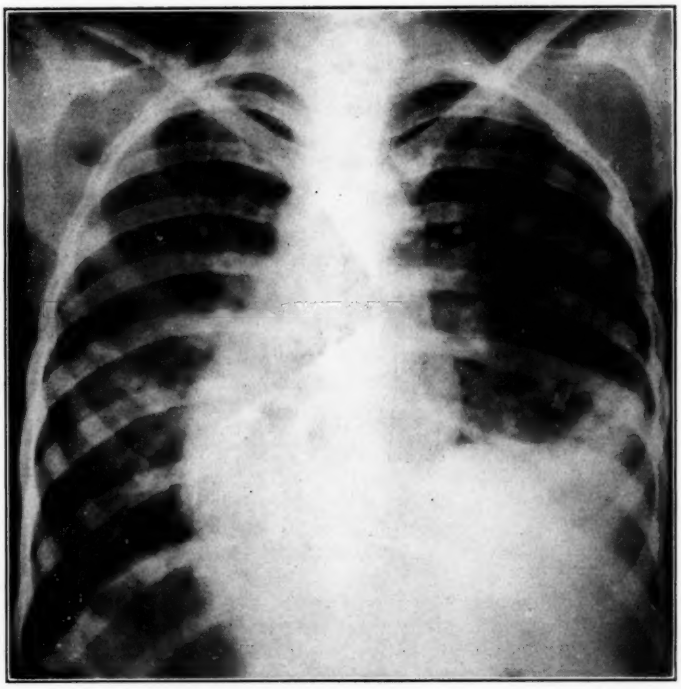

FIG. 2

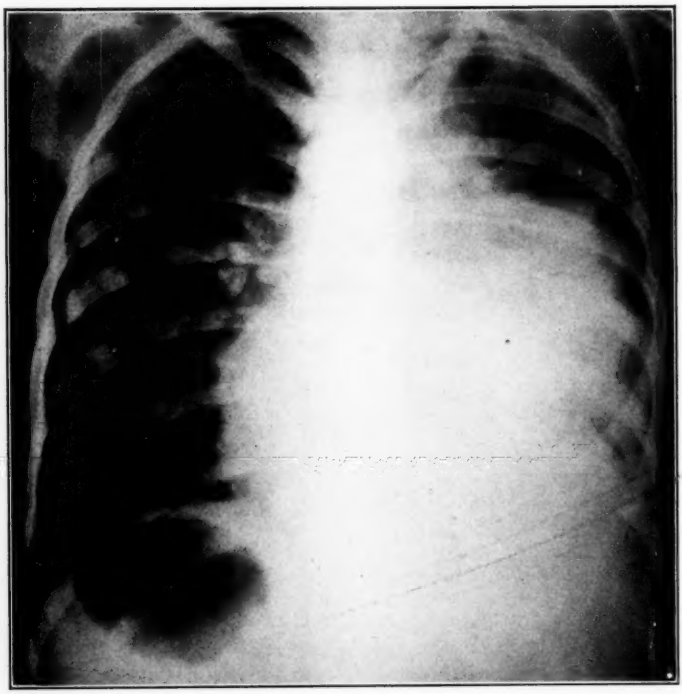

FIG. 3

abscess was made tentatively, but it was not deemed wise to operate at this time. The signs in the chest continued to increase, and several days later another examination with the Roentgen ray showed that while the diaphragm remained in the same position as formerly, there was a mottled density in the right lower lobe, and also evidence of fluid in the costophrenic angle (Fig. 2). Evidences of an increasing amount of fluid in the right pleural cavity appeared, and several days later a third Roentgen ray examination showed that the line of the diaphragm could no longer be seen, and that there was evidence of a well-marked effusion in the chest (Fig. 3). A diagnosis of subphrenic abscess, with extension upward into the pleural cavity and the lung was made. Both the pleural cavity and the subphrenic space were drained. Serous fluid was obtained from the chest cavity and foul pus from below the diaphragm. After the operation the patient made a complete recovery.

Comment. The accompanying illustrations (Figs. 1, 2 and 3) demonstrate clearly the advance of infection in the thorax, once it has been carried upward through the diaphragm. It is presumable that in this case the liver was adherent to the costal margin, because the liver was not displaced downward, nor did the right costal margin move on inspiration.

CASE IV.—W. C., a male, aged thirty-five years, ten days before admission to St. Alexis' Hospital, had a very severe pain in the epigastrium, associated with vomiting. For four days thereafter he had considerable pain and tenderness in the epigastrium. On the fourth day the temperature rose and the patient became worse. The patient was admitted to the hospital ten days after the onset in the following condition: Motion of the right chest was limited; the right costal margin moved not at all; there was flatness from the third rib in front and from above the angle of the scapula behind. Breath sounds were absent. Tactile fremitus was diminished. There were a few moist rales at the right base. No succussion sound was heard. The liver was not displaced downward. The Roentgen ray examination was unsatisfactory on account of the condition of the patient, which was very serious. Based on the history and findings, a tentative diagnosis of subphrenic abscess was made. Operation was performed, and a great deal of foul-smelling pus was evacuated from below the diaphragm, but the patient died. Autopsy showed a perforated ulcer on the upper curvature of the stomach behind and a subdiaphragmatic collection of pus. The liver was firmly adherent to the costal margin. There was a small amount of pus in the right pleural cavity and a beginning bronchopneumonia at the base of the right lung.

Comment. This case shows several points of interest. The process was unusually acute. Autopsy showed that, as a result of the subdiaphragmatic inflammation, the liver was so firmly and extensively adherent to the right costal margin, that any displacement of the liver downward, or any movement of the costal margin was impossible. Here, again, the readiness with which the pleura and lung are involved is well shown. In this case the infection arose in the left posterior intraperitoneal space and spread thence to the right anterior intraperitoneal space.

CASE V.—A girl, aged eight years, was admitted to St. Alexis' Hospital after having been knocked down by an automobile. She had five fractured ribs on the right side and numerous contusions. Physical examination on admission was negative except for the evidence of trauma, and the patient seemed in good general condition. There was some pain in the abdomen, and a specimen of urine showed blood which on the day after admission had increased in amount. Three days after admission the temperature

rose to 104° and the patient ran a high irregular fever for the next three weeks. There was pain, tenderness and rigidity in the upper abdomen. Three weeks after admission the patient passed a large amount of pus in the urine, following which the temperature came to normal. After a few days the temperature again rose. At this time it was noted that there was limitation of motion over the lower portion of the right chest, and that there was flatness over the right base and in the right axilla, and that the breath sounds were diminished. Also a succussion sound was heard in the right axilla. The costal margin flared away from the midline more than normal, and the liver was displaced downward. Roentgen ray examination showed the diaphragm arched to the level of the third rib. The excursion was absent. Below this there was a collection of gas, with a fluid level below it. On these findings a diagnosis of subphrenic abscess was made, which was confirmed by operation. At operation a large amount of pus was evacuated from below the diaphragm. The abscess was retroperitoneal, and apparently arose in the region of the right kidney. The child made a complete recovery.

Comment. In this case the subdiaphragmatic inflammation was secondary to an abscess located either within or around the right kidney. Apparently, the abscess was confined to the right extraperitoneal space. It is interesting to note that the liver was displaced downward and that the movements of the right costal margin indicated a high position of the diaphragm. Because the abscess was confined to the right extraperitoneal space in this case, the absence of any adhesions attaching the liver to the costal margin can be supposed. This would explain the mobility of the liver and the characteristic action of the costal margin.

CASE VI.—M. I., a woman, aged forty-one years, was admitted to St. John's Hospital, with an appendiceal abscess, symptoms of which had been present for a period of about two months. On admission there was a large mass in the right side of the abdomen, characteristic of appendiceal abscess, but there was no evidence of infection elsewhere in the abdomen or in the thorax. The abscess was drained in the usual manner. After the operation the patient continued to run a septic temperature, varying between 100° and 102.5° daily. The pulse stayed in the neighborhood of 120. The respirations rose gradually, until two weeks after the operation, when they were between 35 and 40 per minute. At this time physical examination showed the following condition: The lower portion of the right chest was fuller than the left; the motions of the right chest were limited. The right costal margin moved away from the midline more than the left. Percussion of the right chest showed dulness from the fourth rib in the midclavicular line, from the sixth rib in the axilla and from the angle of the scapula behind. Over this area the breath sounds were distant and a few moist gummy rales were heard. No tubular breathing, egophony, or succussion sounds were heard. The tactile fremitus over the lower right chest was absent. The heart was not displaced. The lower border of the liver was palpable well below the right costal margin.

Fluoroscopic examination showed the right half of the diaphragm at the fourth rib, acutely arched. There was no respiratory motion of the right half of the diaphragm. No air bubble was seen. Films confirmed the shape and position of the diaphragm, and showed in addition some opacity in the right costophrenic angle. There was no roentgenologic evidence of any infiltration at the right base.

On these findings a diagnosis of right subphrenic abscess was made. Operation was performed immediately, and the abscess found and drained. The patient made a marked improvement for three days, and then had

a sudden rise in temperature to 103°, a chill, cough and prostration. On the fourth day after operation the patient coughed up a large amount of foul pus, after which steady improvement in the condition set in. The cough and expectoration of purulent material continued for about three weeks. The subphrenic abscess drained rapidly and the wound closed normally. The temperature fell gradually and steadily. Four weeks after the recognition of the subphrenic abscess the patient left the hospital convalescent. Four weeks later she was examined again. She had gained weight and strength. While some cough persisted, there was little or no expectoration, and both operation wounds had healed.

Comment. This case illustrates the readiness with which infection spreads from beneath the diaphragm upward and into the chest cavity. Although at the time of the operation for the subphrenic abscess there was evidence only of a very slight process in the right pleural sinus and lung (that is, opacity in the right costophrenic angle in the Roentgen ray and rales low down over the right base). The process in the thorax developed rapidly after the operation, and discharged itself through the bronchi. While it is possible that this discharge was from another subphrenic pocket of pus, which ruptured upward, I think this is highly unlikely in the light of the chest findings prior to the operation, and also because a most careful search for hidden pockets under the diaphragm was made at the time of the operation. The movements of the costal margin and the position of the liver were consistent with a subphrenic abscess in this case. It is presumable that the abscess was not in the right anterior intraperitoneal space, and that therefore adhesions had not formed between the liver and the costal margin.

Discussion. The above cases serve to emphasize the fact that subphrenic abscess is of insidious onset, and that early diagnosis is infrequent. On account of the lack of physical signs pointing directly to the subdiaphragmatic location of the infection, the condition is often confused with some postoperative inflammation within the thorax. In each of the cases reported there was dulness, diminished breathing and diminished or absent fremitus on the affected side; in 5 of the 6 cases adventitious sounds pointing to involvement of the pleura, or of the lung, were noted. These signs naturally draw attention to the thorax as the location of the inflammation of the complication. In only 3 of the 6 cases was the outward movement of the costal margin exaggerated, as would be expected to be the case, were the diaphragm in a higher position than normal. In only 3 cases was the liver displaced downward, as would be expected, when a collection of pus lay between the liver and the diaphragm. Therefore these two signs, which when present are important evidence of subphrenic abscess, cannot be depended upon in all cases. As has been pointed out the anatomic location (that is, the particular subphrenic space) of the abscess will determine the presence or absence of these signs. If the abscess be in a position which will cause adhesions between the anterior surface of the liver and the costal margin, then neither of these signs will be present, because the liver will be firmly fixed and, therefore, cannot be displaced downward; on account of its

fixation to the liver the costal margin is held immobile. The presence of a succussion sound and of shifting dulness should always suggest the presence of subphrenic abscess, but these signs are by no means constant. They were observed in 3 out of the 6 cases reported.

The results of Roentgen-ray examination in these cases are of interest. In all 6 it was found that the diaphragm was displaced upward, was more acutely arched than normal and that diaphragmatic motion on the affected side was lost. The loss of diaphragmatic motion seems to be characteristic of subphrenic abscess. Other conditions which enlarge or displace the liver upward may affect the position of the diaphragm, but in such conditions, while the movements of the diaphragm may be limited, they are not lost. It is reasonable to suppose that this loss of motion of the diaphragm in subphrenic abscess is analogous to the loss of motion ("splinting") of the abdominal muscles in intraäbdominal inflammation. Involvement of the pleura and lung may be made out earlier by the Roentgen ray than by physical examination. This is illustrated by the serial observations in Case III. Of course, the value of the Roentgen-ray examination will be vitiated if the process in the lung or pleura be so far advanced as to make a clear observation of the position and of the movements of the diaphragm impossible. While clinical observation and examination should lead one to presume the presence of a subphrenic abscess in all cases, and should enable one to definitely assert its presence in a certain proportion of cases, yet earlier and more positive evidence is to be looked for in the results of the Roentgen-ray examination. Recent articles by Lockwood,[6] Ullman and Levy,[9] Cottle,[10] Douglas[11] and Le Wald[12] confirm the importance of the Roentgen-ray examination.

Obviously, it is highly desirable to drain the abscess before the structures above the diaphragm are involved. In reviewing the subject, as well as in the cases which have come under my own observation, it is striking to note how seldom a diagnosis is made early enough to accomplish this. An early diagnosis of subphrenic abscess can only be established by constant watchfulness for the appearance of this insidious condition and by repeated clinical and roentgenologic examinations.

Conclusions. 1. Subphrenic abscess is not an uncommon sequel to rupture or inflammation of one of the abdominal viscera.

2. Early recognition of subphrenic abscess is difficult. Its onset is insidious, and its physical signs are frequently confounded with those of intrathoracic disease.

3. The movements of the costal margin and the position of the liver may be misleading, depending upon the anatomic location of the subdiaphragmatic inflammation.

4. The most important and the most definite aid to the diagnosis

is the Roentgen-ray examination. Repeated examinations are of the utmost importance, not only in confirming the diagnosis, but also in observing the course of the disease.

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SUMMARY OF PHYSICAL AND ROENTGENOLOGIC FINDINGS IN SIX CASES OF SUBPHRENIC ABSCESS.

	No. of cases present.	Per cent.
Physical signs observed in 6 cases:		
Limitation of thoracic movements	6	100
Asymmetry of chest	3	50
Outward movement of costal margin increased	3	50
Outward movement of costal margin absent	3	50
Percussion dulness	6	100
Breath sounds and fremitus diminished or absent	6	100
Adventitious sounds in lung or pleura	5	83
Succussion sound	3	50
Lateral displacement of heart	0	
Displacement of liver downward	2	33
Roentgenologic findings observed in 5 cases:		
Diaphragm arched and displaced upward	5	100
Movements of diaphragm absent	5	100
Lateral displacement of heart	0	
Subphrenic air bubble, fluid level and splash	3	50
Clouding costophrenic angle	4	80
Infiltration base of lung	4	80

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GENERALIZED TUBERCULOUS ADENITIS WITH REPORT OF A CASE.

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Generalized tuberculous adenitis without other involvement is an extremely rare condition. Following is a case report with a review of the available literature.

History. The patient, F. C., is a nineteen-year-old white male, truck driver, who was first seen on May 17, 1923, when he complained of swelling in front of both ears, under the chin and neck, and a feeling of weakness and loss of "pep." He says he felt well up until about the middle of February, 1923, when he noticed two small masses about the size of a bean in front and below the border of the left ear. There was no pain or tenderness, although the sensation of pressure made him consult his physician. The patient continued at his work for the next two weeks and during this time he gradually noticed increasing fatigue, weakness and loss of ambition. About this time, while accidentally stroking under his chin, he felt small masses in that region also. These were neither painful nor tender, but his general condition became poorer. The swelling started in front of the left ear, then at the right ear, then in the neck. Four weeks after the onset, when examined, he was told that there were similar masses in the axilla, elbows, groins and the back of the neck. These masses kept on increasing in size, reaching the dimension indicated in the physical examination. Following his physician's advice he finally quit working, stayed at home and rested; he drank plenty of milk, and at the time when we first saw him (about two months after the onset) he felt much better, in fact, had no complaints and intended to go back to work.

He lives in Pittsburgh and has been drinking boiled milk supplied by one of the large local dairies. There is no history of cough, expectoration, night sweats, dyspnea or loss of weight, but there is occasional dizziness. Otherwise the history is negative. He has had one attack of tonsillitis, about two years ago.

His habits are good, and he gives no venereal or alcoholic history. He smokes about twenty cigarettes daily and chews about one pack of tobacco per day.

Physical Examination. The patient is a young, well-developed, and well-nourished adult, who does not appear acutely ill. He weighs 143 pounds and is 5 feet 8 inches tall. There is a suggestive puffiness of the face. The temperature during the first three

weeks ranged between 98.2° and 99°, usually higher in the evening, while the pulse ranged from 90 to 100. Eyes, ears, nose and throat are negative. The lungs show no changes beyond the normal variations, except for slight impairment over the right apex, and there are no rales. The heart is not enlarged and shows no murmurs. The blood pressure is 110 systolic and 50 diastolic. The pulse is of good volume and regular and the response to effort is good. The spine, abdomen, genitalia and rectum are negative. The spleen is not enlarged. The nervous system shows no involvement; motor and sensory functions and reflexes are normal. The extremities show the presence of numerous small healed lesions, scarlike in appearance, occurring over the flexor surface of both arms. There is no bronzing of the skin, but a suggestion of osteoarthropathy of fingers.

All the external lymph glands of this patient are involved in a generalized enlargement; the glands on the right are somewhat larger than on the left with only a few exceptions. Nowhere is there any pain, tenderness, local heat or sign of inflammation, or suppuration. There is no scarring, no infiltration of the deep tissues, no matting together, no adherence to the skin. The glands are discrete, variable in size, as will be described later, hard and firm, and usually almond shaped. No signs of pressure are caused by these enlargements except perhaps for some impaired percussion over the right apex, probably due to the pressure of the enlarged right bronchial glands. The anterior auricular, postoccipital, anterior and posterior cervicals, submaxillary, supraclavicular, infraclavicular, axillary, epitrochlear, inguinal and popliteal glands were all palpable and enlarged varying in size from 1½ by 1 cm., to 3 by 2 cm.

Laboratory Examinations. The urine was negative throughout. Hemoglobin and red blood cells were normal; the leukocytes, 5600, with a normal differential. The Wassermann was negative Blood chemistry was normal, as was the electrocardiogram.

The pathological report of excised glands follows: The right epitrochlear gland was first removed. Under low power the section presents a mosaic pattern, which under high power is composed of masses of endothelial cells interspersed with lymphocytes and fibroblasts. An occasional giant cell is found, usually in the center of the group of endothelial cells. The nuclei of the giant cells are placed at one pole. There is no evidence of necrosis. The endothelial cell groups are separated from each other by lymphoid tissue.

The left epitrochlear gland was later removed. The section presents the same picture under low power, but the high power examination differs from the first section, in that the giant cells and fibroblasts are more numerous within the granuloma, and there is beginning encapsulation around each separate tubercle. A diagnosis of tuberculous adenitis was made.

Roentgen-ray examination of the chest on April 9, 1923, by Dr. G. W. Grier was reported as follows: "There is a marked enlargement of the mediastinal glands extending up into the neck. We have never seen tuberculous glands so large or so clearly defined as these. The appearance is more like leukemia or Hodgkin's disease." A second examination on February 9, 1925, showed two glands at the right hilus; there was marked improvement as compared with the former picture.

A tuberculin test was positive. Guinea-pig innoculation with gland material was negative, as were sections of gland stained for tubercle bacilli.

COURSE AND TREATMENT. Soon after the diagnosis was established the patient was placed on high caloric diet and told to stay away from work. He was subsequently seen and treated by Dr. Page, his family physician. Within from four to six weeks he began to feel better, his appetite increased and the temperature came down and remained at the normal level. Gradually, the various glands commenced to decrease in size so that about ten or twelve months after the onset the generalized glandular enlargement disappeared. At present (two years after onset) one can feel several small glands in the posterior cervical region and two in the inguinal region, but no enlargement anywhere else. Patient states he feels absolutely well, is symptom free and has been at his work for some time. The progressive improvement with apparent ultimate cure shown by this patient is not in accord with the prevailing view that generalized glandular tuberculosis is an acutely progressive and fatal disease. The question naturally arises as to whether or not we were here dealing with an infection due to the bovine type of tubercle bacillus.

RÉSUMÉ. The picture presented is that of a young, healthy looking, adult male patient, showing a generalized glandular enlargement, which involved both the external and internal groups of lymph glands; this condition was of gradual onset and of about two years' duration, at first accompanied by slight fever but with no pronounced asthenia, no systemic symptoms, no abnormal blood picture. The glands were discrete, varying in size and there was no tendency to infiltration, no acute inflammation and no suppuration.

DIAGNOSIS. The age, sex, mode of onset, distribution and clinical appearance of the glands, as well as the characteristic involvement of the mediastinum, the negative blood picture, the comparatively slow course, and the exclusion of any of the other more probable conditions, all suggest very strongly Hodgkin's disease. In fact, after studying the case, this was the conclusion reached. And yet, it was felt that because there was no splenomegaly (in 75 per cent of Hodgkin's disease this is found) and because the cervical and mediastinal glands were comparatively not much enlarged, that it might be advisable to excise one of the glands for section. On

FIG. 1.—Low power photomicrograph of left epitrochlear gland.

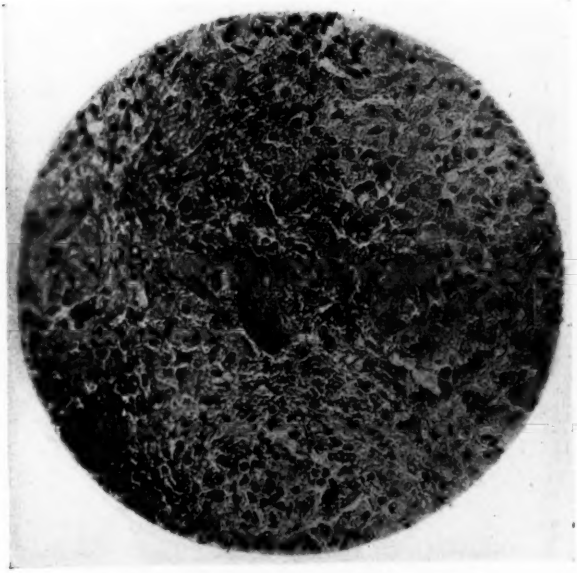

FIG. 2.—High power of section from Fig. 1.

FIG. 3.—Low power right epitrochlear.

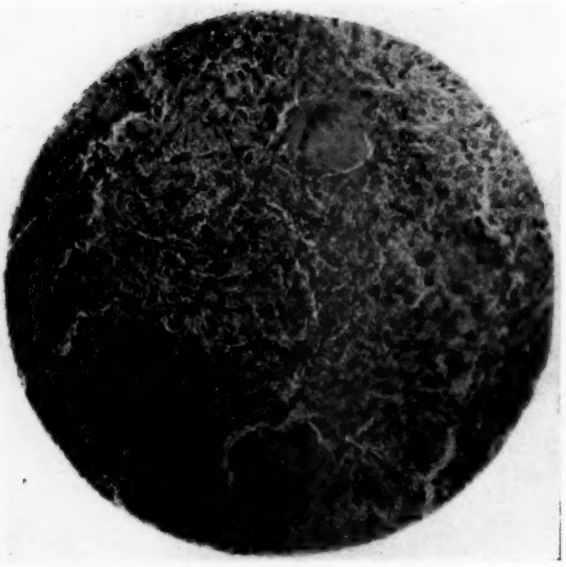

FIG. 4.—High power right epitrochlear.

FIG. 5.—Roentgen ray of chest—marked enlargement of mediastinal glands.

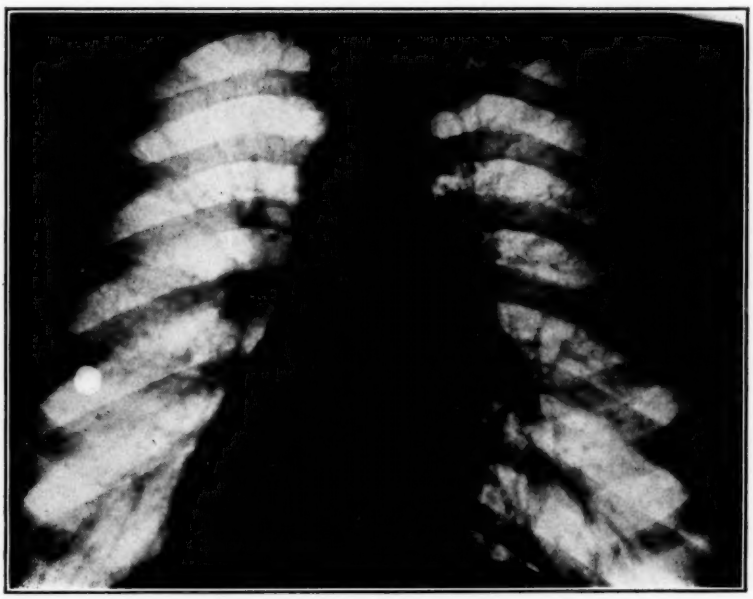

FIG. 6.—Marked improvement with diminution of mediastinal enlargement.

doing this, we selected the right epitrochlear in order to exclude some associated condition that might more likely be found if one of the cervicals were sectioned. The sectioned gland showed a picture typical of tuberculosis as given in the pathological report. In order to make doubly certain, another gland was excised with the same result. Guinea pigs were inoculated with this gland with the idea of demonstrating whether one was here dealing with bovine or human tuberculosis.

Comment. A review of the available literature discloses but few such genuine cases. Most of the reports are meager and more or less confusing: (1) Because the generalized adenopathies have not been recognized as clinical and pathological entities until fairly recently; and (2) because the confusion that existed and still exists as to the etiology of some of these adenopathies still raises the question of entity. The few reports of such cases are not conclusive in that they are not accompanied by biopsy or bacteriologic studies.

It was not until 1845 that Virchow described the blood picture in leukemia, making possible the separation of this disease from other forms of adenopathies. Hodgkin, in 1832, described the glands of the disease which now bears his name, and, for some time since, the question has often been raised as to the relation of this condition to tuberculosis. In fact, clinically at least, generalized tuberculous adenitis is not infrequently diagnosed as Hodgkin's disease. Delafield[1] reported a case of general adenitis which clinically resembled Hodgkin's disease but which at autopsy was found to be one of general tuberculosis involving the lungs, spleen and various groups of lymph nodes. Sternberg in 1898–1899 reported on 13 autopsied cases of Hodgkin's disease, 8 of which proved to contain tubercle bacilli.

Sailer,[3] (1902) from an investigation of the literature, was unable to find any clinical features to distinguish between tuberculous adenitis and Hodgkin's disease, and thought that the entire evidence tended to confirm the supposition that the majority of cases of Hodgkin's disease, if not all, would be ultimately recognized as tuberculous in nature. However, Andrews,[4] in the same year, concluded that while there is a form of tuberculosis of the lymph nodes clinically indistinguishable from Hodgkin's disease (lymphadenoma) yet, Hodgkin's disease is a separate entity not due to the tubercle bacillus. He further brings out the point that histologic and bacteriologic procedures can always settle the question and that a fair number of patients with Hodgkin's disease become secondarily infected with tuberculosis.

This confusion is now almost extinct as a result of the conclusive studies of Reed[5] and others who established the fact that Hodgkin's disease bears no relation to tuberculosis. The entire discussion is of interest because this case as well as one other case reported was clinically diagnosed as Hodgkin's disease and only after histologic studies was the diagnosis of tuberculous adenitis made.

Sabrazes,[6] in 1892, and later Ducion, first demonstrated that it is possible to have generalized adenitis due to tuberculosis: Berger and Besancon in 1899 dealt again with such a type of glandular enlargement, supporting the writings of Schurr, of Vienna, and Tixier Courmont, and Bonnet.[7] But of actual case reports there are but few which present no evidence of visceral tuberculosis.

Tedenat,[8] in 1901, reported the case of an eighteen-year-old male who presented enlarged maxillary, cervical, axillary and iliac glands, verified as tuberculosis by section and innoculation. There was no evidence of tuberculosis in the lungs. In the same paper he reports another case, that of a forty-year-old Italian workingman with enormous glandular masses in the epithrochlear, cervical and all other glandular regions of the body, this condition being accompanied by fever. The patient died in six months and section proved the glands to be tuberculous. Nothing, however, is said about the presence of tuberculosis elsewhere. Delafield, Weisshaupt[9] and Askanazy report similar cases but in none is the evidence convincing as to the absence of tuberculous lesions in any of the other organs. Patton[10] reports from the Cook County Hospital the case of a patient who started with a generalized glandular enlargement, fever, cachexia and few rales in the apices of both lungs. The disease had an acute course and autopsy showed tuberculous involvement of all glands in the body as well as of most of the organs. Goodhart[11] reports another similar case, of acute onset, rapid development and fatal termination. Autopsy, however, revealed tuberculous involvement of many of the organs in addition to the entire glandular system. Buicliu[12] and others likewise report cases showing generalized adenopathy of tuberculous origin, but, invariably, associated with tuberculosis elsewhere. Williamson[14] reports the case of a young nurse who was taken ill suddenly, with fever, malaise and enlarged glands, in the cervical, axillary and inguinal regions as well as some enlargement of the internal group, chiefly the abdominal glands. The course was rather acute and stormy, but after nine weeks of high fever and illness, the temperature began to fall, the glands to diminish in size, and finally became so small that they were not palpable and the patient got well. Biopsy proved the glands to be of tuberculous nature of the bovine type.

The question then arises, what is the relationship between visceral and glandular tuberculosis? Why is it that the glandular system alone will, as in this case, become involved, and what is the method of transmission in these cases?

Regional tuberculous adenitis usually follows on tuberculosis of the organ or organs drained by the lymphatics involved, as mesenteric tuberculosis secondary to tuberculous enteritis. However, tuberculous cervical adenitis is not uncommonly seen without demonstrable primary tuberculous site. It is also true that tubercle bacilli may be engulfed by phagocytes and carried to neighboring

lymph nodes without demonstrable lesions in the viscera. This is one explanation for the frequency of peribronchial tuberculous adenitis without any lesions in the lungs, as seen in this case. In regional tuberculous adenitis it is conceivable that the bacillus may have as its portal of entry the regional mucous membranes or the skin. However, in generalized glandular tuberculosis this explanation does not hold, for, we are here dealing with a systemic involvement for whose dissemination the lymphatic supply or the blood alone can be held responsible.

We know that the tubercle bacillus is conveyed from one part of the body to the other by the blood or lymphatics. How is it then that during this spread none of the viscera will at times become involved? In attempting an explanation one is naturally driven to the conclusion as to the possibility of selective affinity of the tubercle bacillus for certain tissues. Thus, it is argued, Treponema pallidum has been shown to early invade the blood stream and likewise to show affinity for certain tissues, so that, there are patients who show cutaneous manifestations of their infection, while others show visceral, vascular or nervous involvement. Therefore, may it not be possible that varying strains of tubercle bacilli may also have such a selective affinity? The evidence in favor of this supposition is not conclusive.

Tixier, Courmont, Bonnet[7] and others have shown experimentally that guinea pigs injected with material from glands of patients suffering with generalized glandular tuberculosis lived longer than guinea pigs injected with material from the tuberculous meninges of the same patient. Not only that, but the first injected guinea pigs were shown to develop generalized tuberculous adenitis, whereas the second developed tuberculosis of all organs. They seem, therefore, to deduct (1) the presence of a selective affinity, and (2), that glandular tuberculosis is not anywhere near as virulent. However, difference in virulence of tubercle bacilli had never been very clearly demonstrated. This work has not been confirmed by others. Not only that, but Tedenat and his co-workers deduce from clinical experience that generalized glandular tuberculosis is usually fatal. With this opinion Fagge[13] and Goodhart[11] agree. The clinical course of the case here reported does not confirm this view.

Summary. 1. A case of generalized tuberculous adenitis without any visceral tuberculosis is here reported. The condition is getting progressively better and is of two years' standing.

2. Clinically the condition may easily be confused with Hodgkin's disease but biopsy and bacteriologic study will settle the diagnosis.

3. A review of literature discloses but few such cases.

4. There is no explanation as to how the glands may become involved in such process without any visceral involvement.

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SPONTANEOUS RUPTURE OF THE HEART.

A Clinicopathologic Study Based on 22 Unpublished Cases and 632 from the Literature.*

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Spontaneous rupture of the heart is of sufficient rarity to occur but seldom in the experience of a single individual; its dramatic qualities are such, however, that the individual frequently wishes to record his experience, with the result that medical literature contains a comparatively large number of single cases or small group reports. This, together with the coincidence of several cases within a short period at the Philadelphia General Hospital has led us not only to present in detail 22 hitherto unpublished

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cases that could be collected from this and other hospitals of Philadelphia, but also to tabulate the important items of 632 cases from the medical literature of the past fifty years. The incidence of only 7 cases in 16,000 autopsies at the Philadelphia General Hospital is similar to that reported by Romeik at Munich (7 in 13,000 autopsies), but less than the Leipzic series (9 in 8000 autopsies).

The beginning of our search was made with the year 1872. Except for a few cases of historical interest, it was felt that cases prior to 1872 would not have been studied in a sufficiently modern way to fit in with the analysis of the later cases. In 1872 Quain published his important article "On Fatty Diseases of the Heart," which not only presented data on a large series of hearts that had ruptured, but also announced principles that dominated the thought on this subject for many years. In fact some of his statements, misleading rather than incorrect, and hardly possible to have been improved upon in the state of cardiac pathology of that day, are responsible for some of the mistaken views that are held on the subject of cardiac rupture today. Quain was correct in asserting that "Rupture of the heart may be said never to occur spontaneously when the heart is healthy." Accurate on the whole is his description of the appearance of the tear, its relative frequency in the various chambers and in the two sexes, the importance of old age and of most of the symptoms observed. His description of the pathogenesis and the myocardial lesions, however, was very unsatisfactory. Twenty-seven per cent were considered to be due to fatty degeneration and 6 per cent to softening. Ulceration, interstitial hemorrhage, abscess and bursting of an aneurysm were also mentioned, while the coronaries were barely noticed. In modern textbooks of pathology such statements occur as "The most frequent causes are fatty degeneration of the muscle and occlusion of the coronary arteries, less commonly, myomalacia, abscess, gumma echinococcus cysts and new growths are responsible." One of the best pathological textbooks states that spontaneous rupture usually occurs with chronic aneurysma cordis, necrosis following coronary disease, marked fatty infiltration, especially if combined with fatty degeneration or brown atrophy; the latter an obvious "left over" from the days in which the condition of the coronary arteries was seldom reported upon and their significant relation to myocardial lesions apparently not well understood. In the present analysis particular attention is paid to this point, which has also been emphasized by Robin and Nicolle.

Methods. During the past fifty-two years there have been valuable summaries of this subject by Minet and Le Clerc, based on a study of 77 cases; by Robin and Nicolle, based on 177 cases; Quain's 100 cases previously mentioned. These together with the 22 cases of our own series and the 278 cases analyzed by us from the literature make a group of 654 cases on which this study has been based.

Valuable summaries by Elleaume and Barth had to be omitted from our figures, as it was probable that some or many of their cases had been used by Robin and Nicolle. As the latter's cases were tabulated as individuals, we were able to compare them with our lists and thus eliminate 26 duplicates. As Quain's list may also contain some duplicates, though probably few, we have preserved the identity of the main sources in our tables. Thus the reader may select as he chooses, as well as compare the various sources. The 278 cases that we have abstracted from the general literature were secured from 191 references in the *Index Medicus* and the *Index Catalogue* of the Surgeon-General's library.* In each case, as far as possible, information was tabulated about the sex, age, occupation, habits and past history, clinical diagnosis, onset of duration of severe cardiac symptoms, symptoms attributable to the rupture, duration of life after probable occurrence of rupture, whether or not it happened during sleep, if hemopericardium was present, site, size, nature of tear in the myocardium, whether partial or complete, cause of rupture, contributing lesions, condition of coronaries and miscellaneous remarks. It was, of course, impossible to secure all of this information in the three collected reports above mentioned, and even many of the single reports were deficient—an evidence of the inability of the average medical writer to give complete statements on even the simplest subjects. Obviously, too, the results obtained are much more reliable in some particulars than in others. Thus the evidence on such concrete simple items as age, sex, chamber ruptured and so forth can hardly be incorrect and in such large numbers must represent closely the true picture. Other details where the author's judgment is concerned, however, such as "survival after rupture" and "underlying cause," must be taken with greater reserve.

Before considering the results of the statistical study some details of our own 13 cases, which are fairly representative of various types, will be given.†

Case Reports. Our own series of cases can be divided into the following five categories: (1) Coronary sclerosis and thrombosis with myocardial fibrosis and necrosis, 9 cases; (2) coronary sclerosis and thrombosis with myocardial fibrosis only, 2 cases; (3) coronary sclerosis only with myocardial fibrosis and necrosis, 5 cases; (4) coronary sclerosis only with myocardial fibrosis, 2 cases; (5) no evidence about the condition of the coronaries, 4 cases.

Group I. Coronary Sclerosis and Thrombosis with Myocardial Fibrosis and Necrosis. CASE I.—W. L., a senile dement, aged seventy-nine years, was admitted to the Psychopathic Department of the Philadelphia Gen-

* References to these cases are too numerous to be included here, but will be furnished by the authors on request.

† It has not been possible to copy the exact words of the autopsy reports in all cases. The authors' therefore assume responsibility for the statements made.

eral Hospital, November 7, 1923, on the service of Dr. Rhein. No history of heart disease was obtained, though his feet were edematous, his heart sounds weak and peripheral vessels sclerotic. No murmurs, arrhythmia or cardiac enlargement were found. Urine and blood Wassermann tests were negative and the blood urea was 19 mg. The blood pressure was not taken. His condition continued unchanged until 1.30 A.M. of November 24, when he was found dead in bed, without the patients in the next beds having noticed anything unusual. Thirty minutes earlier he had talked normally with the night nurse.

At autopsy (P. G. H., 8236) I found the pericardial sac bulging with fluid and clotted blood (totaling over 350 cc.), which was found to be due to a small jagged opening, about 6 mm. long, in the posterior surface of the left ventricle, and slightly nearer the apex than the base. This did not at first admit a probe without danger of causing an artefact, but after the heart was opened it was found to connect diagonally with a similar opening in the endocardium near the posterior papillary muscle of the mitral valve and to admit easily a small probe. At neither point was there any clot. The heart weighed 400 gm. and measured 12 by 9 by 7 cm. It showed a thick, fatty, epicardial layer, with prominent and tortuous coronary arteries and mottled myocardium; toward the apex this almost resembled the scar tissue of a healed infarct. The muscle was flabby, but not tough. There were no pericardial adhesions. The right ventricle was apparently normal, its wall averaged 4 mm. in thickness and it contained a small amount of mixed red and white clot. The mural endocardium of the left ventricle was especially thickened at the lower end of the septum, and the myocardial wall was thinner at this point (6 to 8 mm.). The myocardium elsewhere measured from 10 to 14 mm. in thickness and showed no noteworthy fibrosis except in the area mentioned. The tips of the papillary muscles and chordæ tendineæ were very slightly thickened. The mitral and aortic valves were slightly thickened. The valve orifices measured: Mitral, 10, aortic, 7½, tricuspid, 10, pulmonary, 7 cm. The orifices of the coronary arteries were somewhat sclerosed, especially the left. The right coronary artery, about 2 cm. from the orifice, was occluded with a dark red adherent clot, extending into the two branches for several centimeters.

Anatomical Diagnosis. Hemopericardium. Acute infarct of myocardium with rupture following coronary thrombosis. Myocardial degeneration with cardiectasis due to coronary sclerosis.

Other items of interest in the autopsy were a markedly atheromatous and fragile aorta, a phlebolith in the splenic vein, chronic splenitis and mixed nephritis, cerebral arteriosclerosis, thrombotic softening and convolutional atrophy.

Histology. Heart: Left ventricle: The subpericardial fibers are best preserved, though even here they are cloudy and swollen with indefinite striæ. There is some fragmentation and pigmentation, the nuclei are found to be large and rectangular. Deeper, these phenomena are more prominent and interstitial fibrosis appears, with much distortion of muscle fibers, several areas of fibrosis, containing but few muscle remnants, fill whole low-power fields. Fibrosis is most marked about the vessels. Serial sections through the ruptured area of the ventricle show a complicated picture of muscle degeneration, anemic infarction and, at a distance from the rupture, a separate, partly organized infarct. The jagged, oblique sinuous line of rupture can easily be traced through a definitely necrotic space, in an irregularly flat pyramid with the apex almost at the pericardium. The fibers are traversed in their long axis near the endocardial surface by the rupture, but transversely through a narrow subpericardial band.

The path of the rupture is lined by the bare fibers in some places, in others by a smooth composite of necrotic and interstitial tissue and infiltrated cells of various kinds. No thrombi are present. The tissue in which the rupture lies presents in a more marked degree the same lesions as more distant areas, but so close to one another that a continuous line of lessened resistance resulted. At some points, reaching almost to the line of rupture, the muscle is merely swollen and wavy, with more or less loss of striæ and tendency to pyknosis of muscle nuclei. There is considerable perinuclear pigment and some hyaline and fatty degeneration. At other places there has been marked complete loss of muscle fibers, giving a lacework appearance to the interstitial tissue, and this may be with or without cellular infiltration. Many areas have a dirty, slate-blue appearance (with hematoxylin and eosin), due to infiltrated polymorphonuclears, macrophages, some erythrocytes, etc., and much nuclear débris. These areas may be fairly massive or insinuated between the muscle fibers. A few zones, distant from the rupture, show beginning organization (numerous fibroblasts and capillaries, and pigment-laden macrophages). Peripheral zones of hyperemia are conspicuous by their absence. Still rarer are the areas of true anemic necrosis, that is, where the outline of the muscle fibers is preserved, but all structural detail and nuclei are lost. The same picture of marked perivascular fibrosis is present here, as in the other parts of the myocardium. Right ventricle: There are some changes in muscle fibers, but less marked. There is no marked fibrosis, though loose fibrous tissue and fat occur between the fibers.

Histologic Diagnosis. Coronary sclerosis and thrombosis, anemic infarct of myocardium; chronic interstitial myocarditis (perivascular). Organizing infarct.

Comment. The interesting features in this case are that rupture occurred during sleep, when there should have been the least amount of strain on the heart wall, and that it occurred in an unusual position, where the obvious chronic lesions were less advanced, but where the acute lesions were fraught with much greater danger, though not detectible by the naked eye. Although the myocardium grossly appeared the same as in many other localities, the microscopic picture clearly shows that following the recent coronary thrombosis (of at most a few days' duration), an anemic necrosis occurred, which offered less resistance that the more chronically injured tissue. From the obliquity of the tear it must have been, more or less, closed during systole, but allowed the blood gradually to escape during diastole until it so filled the pericardial cavity that the action of the heart was stopped. In regard to the supposed freedom from strain during sleep, MacWilliams has recently offered some interesting data which will be discussed later.

Case II.—M. McB., aged about seventy years, a helper in the kitchen of this hospital, while at his usual work of peeling potatoes, complained of feeling badly, with a pain over his heart (May 26, 1924). A few minutes later he vomited and fell forward in his chair unconscious. His face became very blue, and his breathing stertorous. An intern who made a hasty examination could not hear his heart sounds at this time, and his lungs soon became filled with the coarse bubbling rales of pulmonary edema. He died less than five minutes after reaching the medical ward (Dr. Musser) and probably about fifteen minutes after his acute symptoms developed. Though elderly and rather feeble, previous to this he was not known to have been in poor health in any way.

Autopsy. (P. G. H., 8853, Dr. Eiman.) The pericardium extended 5 cm. to the right of the midline and practically to the ribs on the left. It contained 420 cc. of blood (partly in the form of currant-jelly clot).

The heart weighed 395 gm., measures 14.5 by 10 by 5.5 cm. and was of a peculiar, blunt, quadrangular shape. There were excessive amounts of pericardial fat, especially on the right side, the auricles were dilated, the ventricles contracted. A jagged, irregular tear, 7 mm. long, was found 3.4 cm. above the tip and 4.5 cm. to the left of the anterior coronary artery (that is, near the left border). The probe passed through this tear without any resistance into the left ventricle, where it was found to have traversed the split base of one of the mitral's papillary muscles. The myocardial wall, which here measured 11 mm. in thickness was mottled brownish-red, with areas of brighter red and small irregular streaks of a tarry substance were found in their centers. The myocardium elsewhere was cloudy and brown in color. Its walls varied in thickness from 5 mm. at the tip of the left ventricle to 20 mm. in its thickest portion, the right ventricle was 5 mm. thick. The valve leaflets showed no noteworthy lesions; they measured as follows: Mitral, 9.3 cm.; aortic, 6.3 cm.; pulmonic, 7.5 cm.; tricuspid, 12.3 cm. The coronary arteries were greatly fibrosed and calcified; the anterior descending branch just above the site of the rupture had practically no lumen left, and was completely filled with red clot.

Anatomical Diagnosis. Hemopericardium. Acute suppurative myocarditis with rupture. Marked coronary sclerosis and thrombosis (?) of anterior descending branch. The other lesions noted were chronic fibrous changes in the pleura, spleen, kidney, pancreas and aorta, and a small right testicle with absence of left testicle and feminine body proportions and hair distribution.

Histology. Heart: Immediately beneath the normal epicardium and thick fatty layer the fibers (cut in cross section) have a relatively normal appearance, except that in some areas there is considerable replacement with fibrous tissue. About 2 mm. deep there is a grossly visible blue staining zone, due to the occurrence of polymorphonuclear leukocytes and tissue débris, packed between the muscle fibers and grouped in circular areas. No bacteria can be found, even with special stains. The fibers here are narrowed by compression and either partly or wholly necrotic. For the remaining depth of the section (that is, as far as the endocardium), the muscle fibers, though not compressed, are wholly or partly necrotic, and frequently surrounded by clumps of detritus and leukocytes. The Purkinje fibers are excessively prominent, swollen and apparently necrotic.

Histologic Diagnosis. Acute infarct with liquefaction necrosis, due to coronary thrombosis.

Comment. The clinical history of this case is rather typical and illustrates some of the difficulties of proper study. Differential diagnosis from fatal coronary thrombosis would have been impossible. The absence of any known previous illness, especially in view of the lesions found, is noteworthy, though not infrequent.

The gross and microscopic signs of acute inflammation suggest that the heart may have been predisposed to rupture by bacterial suppuration; but in the absence of demonstrated bacteria and the presence of coronary thrombosis, it seems more probable that the necrotic infarct had liquefied and that the leukocytes were attracted by the sterile process.

CASE III.—M. F., an obese Irishwoman, aged fifty-seven years, was admitted to the nervous department of this hospital on Dr. Pemberton's service on August 14, 1902, with the diagnosis of left-sided hemiplegia. There was nothing noteworthy elicited in her family and past history. Her present illness had come on during sleep, four weeks before, with inability to use her left arm and leg, but without speech disturbance. This condition had persisted without much improvement. Her pulse was rapid and sclerotic; there were no cardiac murmurs. Her urine was nega-

tive. On January 31, 1905, she went to bed feeling as usual. During the night the nurse noted that she had become cyanotic and that her breathing was stertorous and a few moments later she died.

Autopsy. (P. G. H., 440, Dr. Funk, twenty hours postmortem.) The pericardium contained a considerable amount of fluid and clotted blood. The heart was relatively small, weighing 350 gm. with a heavy layer of subpericardial fat. On the posterior surface of the left ventricle, 3 cm. above the apex, was a laceration, 15 mm. long and 5 mm. wide, parallel to the long axis of the heart. Near the rupture were numerous hemorrhages in the pericardial fat and a soft greasy yellow-pink area which occupied almost half the ventricle. The line of rupture was jagged and tortuous, reaching the endocardium just posterior to the base of the anterior papillary muscle. There was no evidence of scar tissue formation. The coronary arteries were markedly sclerosed. The lumen of the right coronary was especially diminished and contained clotted blood, which was probably an antemortem thrombus.

Anatomical Diagnosis. Hemopericardium. Rupture of posterior wall of the left ventricle, due to acute infarction (?) following coronary thrombosis. (At the time of autopsy this was termed local fatty degeneration.) There was also found cirrhosis of the liver and chronic parenchymatous nephritis.

Histology. Sections were not taken at the time of autopsy, but nineteen years later when the heart was first opened. Section of the posterior descending branch confirms the marked sclerosis with great narrowing of the lumen. Smaller branches near the rupture are totally occluded with dense fibrous tissue. The muscle adjacent to the line of rupture is much fragmented, and shrunken or wavy and disintegrated with loss of striæ and nuclei. The areas of necrosis are not extensive, however. There is no cellular infiltration, except for clumps of erythrocytes in the epicardial fat, and there is only a slight layer of fibrin almost free from cells. The muscle cells immediately adjacent to the line of rupture contain much golden pigment (hemosiderin?). There is considerable periarterial fibrosis.

Histologic Diagnosis. Coronary sclerosis and fibrous occlusion. Myocardial fibrosis with areas of necrosis.

Comment. This presents the usual clinical history and pathologic picture of coronary disease with myocardial degeneration, followed by thrombosis of a branch with infarction of the stricken area, and in turn by spontaneous rupture.

CASE IV.—M. K., an obese nervous white woman, aged fifty-eight years, was admitted to Dr. Burn's service of the neurological department of this hospital on August 27, 1923, with a diagnosis of right-sided hemiplegia. She complained of "nerves," and said she had had "neuritis" of her left arm and leg for two years. She denied any past illnesses, had had five children, two miscarriages and had a negative Wassermann reaction.

Physical examination showed the usual signs of an old hemiplegia, with equal pupils, partial aphasia and paralysis, and emotional instability. The heart dulness was slightly increased with a faint, apical, systolic murmur, not transmitted, and weak distant sounds. The urine showed a trace of albumin, but no casts and the blood chemistry was negative.

Except for persistent constipation, the patient continued the same for eight months, without any signs of cardiac decompensation. Suddenly at 1 A.M., while lying in bed, she became pulseless, very cyanotic and dyspneic, and died within fifteen minutes. When seen by the intern she was unconscious, though only fifteen minutes before the attack she was complaining merely of weakness and was somewhat dyspneic.

Autopsy. (P. G. H., 8772, Dr. Lucke, twelve hours after death.) The pericardial sac was distended with about 300 cc. of frothy clotted blood. The heart was of normal shape and somewhat enlarged, weighing 520 gm., and measuring 14 by 11 cm. There was much epicardial fat, varying from 4 mm. at the left apex to 8 mm. in thickness at the left base. Just above the tip of the right ventricle there was a slight bulging of the epicardium, due to a diffuse irregular hemorrhagic infiltration, roughly 4 cm. in diameter. Section here showed the epicardial fat to be 6 mm. thick over a thin strip of muscle, which varied from 1 to 2 mm. in thickness. In many places the fat extended into the left ventricular wall, especially in the bulging hemorrhagic area, where there was an irregular tear, 2 cm. in diameter, communicating with the right ventricle. The neighboring tissue was densely infiltrated with blood. The left ventricular wall averaged 23 mm. in thickness, but here thinned out to 6 mm. A walnut-sized thrombus adhered to the left apex. The chordæ tendineæ and papillary muscles were normal; the mural endocardium slightly thickened, especially below the aortic ring. The aortic leaflets had slightly stiffened, atheromatous bases, the valves otherwise being normal and measuring: Aortic, 8; mitral, 10, tricuspid, 12.5, pulmonary, 8.2 cm. The coronaries were somewhat tortuous and had an irregularly thickened intima. In the right coronary (the walls of which were much more diseased than the left and were thick, distorted and crumbling), a firm red clot filled the lumen, beginning about 2 cm. from its origin. Both descending and horizontal branches contained the same kind of clot as far as could be traced. It was not possible to ascertain the primary site of thrombus formation. A branch from the main artery (given off before the main descending branch) was pointing straight for the rupture. This also was filled with red clot, but became too small to trace grossly before the rupture was reached. The muscle in this area did not vary grossly from the myocardium elsewhere.

Anatomical Diagnosis. Hemopericardium. Rupture of right ventricle. Coronary sclerosis with thrombosis of right branch. Hemorrhagic infiltration of apex with thinning of walls of both chambers. Antemortem clot in apex of left ventricle.

Histology. Large areas of fibrin, erythrocytes and cellular débris merge inextricably with muscle fibers in various stages of distortion and degeneration. In the less changed areas the muscle fibers are compressed between hemorrhagic infiltrates and numerous polymorphonuclears. There is marked evidence of scavenging and new tissue formation with many phagocytes, plasma cells, eosinophils and beautiful "polyblasts," with relatively few new bloodvessels. The larger branches of the coronaries are much sclerosed and distorted and many filled with antemortem clot.

Histologic Diagnosis. Coronary sclerosis and thrombosis. Extensive necrosis of myocardium with beginning repair.

Comment. The rupture of the right ventricle accords with the thrombosis of the right branch. The extension of the necrosis into the left apex indicates that in this case the posterior descendens supplied more than its usual amount of myocardium. Correlation of clinical and pathological evidence shows that the coronary thrombosis (which from the histological picture must have occurred at least many hours before death) gave no signs or symptoms and that the terminal symptoms followed the actual rupture of the ventricular wall.

CASE V.—A man, aged thirty-eight years, of dissolute habits, during a drunken debauch at Atlantic City fell heavily against a box for mixing mortar, hitting the edge against his precordial area. When seen by Dr. Henry Marvel, several days later, he had considerable precordial pain,

but no diagnosis was made. No further details are now available except that death occurred suddenly.

Autopsy. (U. of P. Dept. of Pathology, No. 345.) The pericardial cavity was filled with clots of blood. About half way up the outer wall of the left ventricle in the visceral pericardium was a transverse tear, 3 cm. in length, which extended into the myocardium for about two-thirds of its depth. No mention is made of the coronaries grossly, but histologically the arterioles were reported as occluded and the myocardium near the rupture as acutely necrotic. (As Dr. Marvel's records were not available, the autopsy notes, supplemented by verbal statements of Dr. A. J. Smith, have been used with his kind permission.)

Comment. It is more probable that trauma played a prominent part in this case, but that it acted by injuring the coronary with subsequent thrombosis formation and that rupture occurred "spontaneously" as a result of the thrombosis.

CASE VI.—A housekeeper, female, aged sixty-five years, entered the Peter Bent Brigham Hospital at 9 A.M., and died suddenly at 5 P.M. She had had dyspnea for ten years and for more than a year had many attacks of sharp precordial pain, most apt to come on during excitement. Her chief complaint was of pain over the heart and in the stomach; she has had pneumonia but no rheumatic fever.

Autopsy. (P. B. B., No. 1744.) The pericardial cavity contained a dark purple clot which surrounded the heart like a cast. On removing this a small rupture of the left ventricle was found situated just to the left of the septum anteriorly, about 4 cm. below the base. This area of rupture measured about 1 cm. in length, was red and the margins fragmented. On the left side of the heart were numerous, rather fresh, friable mural thrombi situated over the lower half of the septum and apex, about the area of rupture. From the ventricular side this area of rupture gave the impression of a punched-out brick, which admitted the tip of the little finger halfway through the musculature of the heart. There were yellow and rather pale mottlings of the myocardium in this region, more suggestive of fat than of actual necrosis. There was no obstruction or narrowing of the orifices of the coronary arteries. On opening the anterior coronary artery which fed the area in which the rupture occurred there were several mural thrombi found on the intimal surface, the first being about 2 cm. beyond the orifice. Some of these were firmly adherent, paler and apparently considerably organized.

Anatomical Diagnosis. Coronary thrombosis. Rupture of myocardium of the left ventricle. Hemopericardium.

Histology. In certain areas the vessels are markedly congested and are surrounded by masses of blood. In these areas the muscle fibers are necrosed, and have among them a moderate polymorphonuclear exudate. This is apparently about the point of rupture. Numbers of small clumps of bacteria (pyknotic nuclei ?*) are also present here. The muscle fibers in other areas show a moderate degree of fragmentation.

Comment. The cause of rupture was evidently due to acute massive necrosis of myocardium caused by either embolus or thrombus.

CASE VII.—A man, aged seventy-one years, the owner of a general store, entered the hospital complaining of pain in the epigastrium, of six weeks' duration. The pain radiated to the chest, usually lasted about three minutes and was sometimes relieved by rest. It bore no relation to meals. He had vomited three times. The last attack, which began on the morning of admission, began in the epigastrium and radiated to chest, right shoulder

* Authors.

and arm. About two hours after physical examination the nurse found him gasping for breath and he stopped breathing shortly after.

Autopsy. (P. B. B., No. 19101.) The pericardial cavity contained 350 cc. of bloody fluid. About the auricle, posteriorly, were large masses of clotted blood. The heart weighed 430 gm. On the anterior surface of the left ventricle, about 2.5 cm. from the apex and running downward and to the left, was an oblique linear rupture of the pericardium and myocardium just at the left of the interventricular septum, but visible on the endocardial surface, as only 1 cm. in length. The softened area about this rupture was supplied by the descending branch of the left coronary artery. About 2.5 cm. above the softened and discolored portions of the left ventricle this vessel was occluded by an atheromatous plaque which had become ulcerated with formation at that point of a dark red thrombus, about 4 mm. in length. No thrombi were demonstrable in other coronaries. The myocardium of the left ventricle in the softened area was found to be pale in several places, and particularly beneath the epicardium were several yellowish-white, irregularly shaped areas, from 2 to 8 mm. in size, suggesting anemic infarcts.

Anatomical Diagnosis. Infarction of the left ventricle with rupture and hemopericardium; thrombosis of descending branch of left coronary artery.

Histology. The cardiac muscle is degenerated and fragmented. At places it shows marked hyaline degeneration with infiltration of few leukocytes and fat globules.

Comment. None.

CASE VIII.—A housekeeper, female, aged seventy-four years, on her first admission, which occurred a year previously, was discharged with a diagnosis of lobar pneumonia, thrombophlebitis and hypertension. She entered this time with a complaint of dyspnea. She had had two or three marked attacks of severe dyspnea and vertigo during the past year. On the day before entrance she was found sitting in a chair in an aphasic condition. A short time later a sharp pain was noted over the precordium. While in the hospital she suddenly began to cough, and died.

Autopsy. (P. B. B., No. 2164.) The pericardial cavity contained 150 cc. of bright red fluid and a large amount of blood clot. The heart weighed 410 gm. Over the anterior surface of the left ventricle and a portion of the right ventricle there was a reddish, granular exudate over an area about 5 cm. across, which was darker than the rest and surrounded a rent in the visceral pericardium which measured 3 cm. in length. This rent began 2 cm. below the pulmonary valve, and extended downward in a vertical direction. Upon making coronal sections a diffuse hemorrhage beneath the pericardium was found surrounding the opening. More coronal sections 3 cm. apart showed this rent to be an irregular slitlike opening, extending outward from the myocardium. It was located in the upper portion of the left ventricle in the tract of the anterior descending branch of the left coronary artery. The total area involved part of the anterior wall of the left ventricle and a portion of the septum downward to within 5 cm. of the apex. A small conical thrombus was found about 2 cm. below the origin of the anterior descending branch of the right coronary. In the wall of the left ventricle there was a large, adherent, friable mural thrombus.

Anatomical Diagnosis. Ruptured infarct of left ventricle. Thrombosis of anterior descending branches of the left coronary artery. Hemopericardium.

Histology. "The picture is that of necrosis superimposed on a myocardium with many cicatrices. There is very marked destruction of

muscle in places with accumulations of polymorphonuclears and débris that give the appearance of abscess formation."

Comment. A typical case, with an interesting association with a probable cerebral thrombosis shortly before.

CASE IX.—A man, aged sixty-three years, the superintendent of a dry-goods store, one year ago noticed that he occasionally was able to hear his heart beating somewhat irregularly. These attacks came on after excessive irritating and nervous work, and there was no associated dyspnea. He tired more easily than usual. He never noticed swelling in the feet or pain in the chest or other symptoms. Two weeks before admission the patient underwent some unusual strenuous exercise and the following day at 10.30 he suddenly felt a sensation of heaviness in the chest, unassociated with palpitation or dyspnea. It gradually became worse, and the patient was forced to pace about in agony, being unable to lie down. After continued pain in the chest and one very bad attack, he was admitted to the hospital, and died suddenly in the morning when raising himself in bed, after spending a comfortable night.

Autopsy. (P. B. B., No. 22100.) About 750 cc. of blood and blood clot was found in the pericardial cavity. Several light reddish-gray, somewhat friable clots, probably antemortem, were also present. There was a rent in the heart muscle on the anterior surface about 3 cm. from the left border of the heart and 8 cm. from the apex. The apex of the heart was soft and discolored. The heart, plus the clot, weighed 800 gm. (net, 700 gm.). The left ventricle was markedly dilated and had an aneurysmal dilatation at the apex, about 6 cm. in diameter. This dilatation was filled with a pinkish-red, granular, friable clot, evidently antemortem. The wall was extremely thin at this area, measuring 5 mm. in thickness. The thinning of the left ventricle began on the posterior wall, just below the attachment of the posterior papillary muscle. The intraventricular septum was apparently not involved. The left coronary artery had an arteriosclerotic lesion on the anterior surface of the heart about 1.3 cm. from its origin. At this portion there was a small pinkish-gray clot, about 1 mm. in diameter, probably a thrombus. The descending branch of the same artery was completely sclerosed a short distance from its origin. The right coronary was apparently normal.

Anatomical Diagnosis. Aneurysm of apex of the heart with mural thrombus. Rupture of the heart. Infarct of the heart. Hemopericardium. Obliteration of left descending coronary artery.

Histology. Some sections taken through the aneurysmal dilatation show extreme infarction of heart muscle, in which the entire musculature has been converted into a structureless débris, eosin staining, and in which are scattered nuclear fragments and an occasional polymorphonuclear leukocyte. In a section showing infarct and adjacent heart muscle, the fibers are pale, the nuclei are fragmented and some of the bundles of muscle fibers are necrotic and converted into a granular acid-staining débris. Between the muscle bundles is an increased amount of connective tissue. Young fibroblasts are seen in some areas. Dense scar tissue is also present.

Comment. This case offers an interesting correlation of clinical and pathological findings. Although the aneurysmal dilatation was infarcted, the actual rupture occurred slightly higher up.

Group II. Coronary Sclerosis and Thrombosis with Myocardial Fibrosis Only. CASE X.—G. S., a busy surgeon, aged sixty-two years, of good habits and health, complained for several days of pain in his upper abdomen, but it was not sufficient to stop him in his active practice. He had a good past history, except that he had been known to have a moderate

amount of arteriosclerosis with hypertension for several years. He neither smoked nor drank. The morning of his death his discomfort was sufficient to keep him in the house, and soon developed into a "terrible oppression" in his chest, together with extreme restlessness, which persisted in spite of liberal doses of morphin hypodermically. This continued for about four hours, when he gasped and suddenly died.

Autopsy. (Presbyterian Hospital, No. 2, 1922, Dr. Eiman, after embalming.) The pericardial cavity was found distended to its utmost capacity with dark red soft clotted blood. The heart weighed 420 gm., was rather pointed and contracted and measured 14 by 8.5 by 6.8 cm., and showed considerable subepicardial fat. On the lower anterior surface of the left ventricle, 3.5 cm. above the tip, was an irregular hemorrhagic area, 3 by 2.5 cm., in the center of which was a jagged rent, less than 1 cm. in length. A probe was passed without resistance into the left ventricle. On opening the left ventricle, at the angle of the septum and the anterior wall near the apex, there was found a soft, partly organized mural thrombus, measuring 6.5 by 2.3 by 1.8 cm. The portion of the wall to which the thrombus was attached was slightly bulging and concave. The inner aspect of the rupture was hidden in the mural trabeculæ, near the attachment of the thrombus, but was found to be smaller than the outer. The left ventricle was 5 mm. thick at the aneurysm, and 20 mm. at the base; the right ventricle, 7 mm.; the auricles, 1 to 2 mm. The myocardium was toughened and discolored by the embalming, but was firm and apparently normal. Even the thinner portion still had considerable muscle tissue left. The pulmonic valves were normal; the others slightly thickened.

The left coronary artery divided anomalously less than 1 cm. from its origin. The branches, which were almost parallel for several centimeters were uniformly thickened and considerably calcified, but with ample lumina. Where the descending branch passed over the elevation of the base of the left ventricle its lumen suddenly narrowed to about 1 mm. in diameter and from there on was filled with a firm dark clot, which extended into the branch that supplied the ruptured area. This thrombosis probably occurred shortly before death. No thrombus was found in the right coronary. The valves showed no noteworthy lesions except for slight thickening along the edges of the mitrals, the bases of the aortic leaflets and diffusely in the tricuspids.

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle following thrombosis of the descending branch of the left coronary. Beginning apical cardiac aneurysm. Anomalous left coronary artery.

Histology. Muscular elements are surprisingly well preserved in sections from all chambers. The amount of perivascular fibrosis is moderate, about the same in all chambers and about what would be expected at sixty-two years. It is slightly greater in amount near the rupture. There is some perinuclear pigmentation. The main coronary branches show a disproportionate amount of sclerosis (more than the renal and much more than the aorta). Some lumina are filled with antemortem clot. Section from the edge of the rupture shows considerable hemorrhagic and some leukocytic infiltration but no evidence of necrosis. No ruptured fibers are seen in the section, and at this level the opening was caused by separation rather than rupture of the fibers. Section from the bulging thinned area shows pressure atrophy of the fibers, but surprisingly little degeneration and fibrosis.

Histologic Diagnosis. Marked coronary sclerosis and recent thrombosis. Perivascular fibrosis of myocardium. Pressure atrophy at dilated area and hemorrhagic infiltration.

Comment. In this case, in spite of the relatively small amount of perivascular fibrosis found microscopically, coronary disease was undoubtedly

a factor in the beginning of cardiac aneurysm. The coronary thrombosis, though it was too recent to show any signs of organization, or even to cause visible changes in the myocardium, was apparently a factor in further weakening the myocardium to the point of rupture. The course of the anomalous coronary apparently predisposed it to sclerosis; what further influence the anomaly may have had is not determinable.

CASE XI.—A housewife, aged sixty-one years, was admitted to the hospital, December 23, 1924, because she had been "out of her head" for the past twenty-four hours. History given by her husband: Mother died of diabetes, aged seventy-eight years; one sister had diabetes. Her past history was negative prior to the present illness, except for impaired hearing in the left ear in the last three years, associated with some earache and buzzing in that ear. Her present illness began two years ago with loss of weight (from 160 to 130 pounds in six months), increasing weakness, great thirst and hunger. Sugar was found in the urine. Her appetite was excessive and there was marked polydypsia. Three days before admission the patient became so weak that she went to bed. The second day before admission she became unconscious and the respirations labored. In the first nine hours following admission the patient received 120 units of insulin with some cereal and milk. The patient then seemed much better and was breathing quietly. She had a good night and in the morning seemed much improved. At 7.10 A.M., without any warning, or noticeable distress, the patient died.

Autopsy. (P. B. B., No. 24100.) The pericardial cavity contained a large amount of blood clot, weighing 115 gm. The heart was distinctly enlarged and weighed 340 gm. On the posterior surface of the left ventricle, just to the left of the intraventricular septum, an irregular yellowish-white area of scar tissue was seen, 2 cm. in greatest dimension. In the center of this area was a slitlike opening in the heart wall, 4 mm. in length, with ragged edges. The heart wall surrounding the opening was represented by a layer of fibrous tissue about 2 mm. in thickness. On viewing the heart wall from within, a definite hole was seen in the myocardium, with ragged, necrotic edges, large enough to admit the tip of the finger. The right coronary artery at a point 3 cm. from its origin was occluded by a definite thrombus 8 mm. in length and grayish-red in color. This thrombus was evidently of recent origin. The artery was found to lead into the area of infarction described above, where its lumen was lost. The left coronary was negative.

Anatomical Diagnosis. Infarction of heart. Rupture of left ventricle at site of infarction. Thrombosis in right coronary artery (recent). Hemopericardium.

Comment. Another typical case associated with a cerebral lesion.

Group III. Coronary Sclerosis Only with Myocardial Fibrosis and Necrosis. CASE XII.—W. M., a man, aged seventy-four years, was admitted to the service of Dr. Riesman, in this hospital, October 16, 1911, with signs of heart failure. The brief history showed that he was a hard drinker and had had most of the contagious diseases but denied venereal disease. He soon developed severe precordial pain, acute dyspnea and cardiac arrhythmia, which progressed to true angina pectoris, Cheyne-Stokes respiration and death on the fourth day after admission.

Autopsy. (P. G. H., 2852, Dr. Ellis, eleven hours after death.) Autopsy showed 1100 cc. of blood in the pericardial cavity. The heart was fairly large, weighing 570 gm., with a moderate amount of epicardial fat. On the anterior surface of the left ventricle near the septum, and 2 cm. from the apex, was a slightly angular tear, 7 mm. long, roughly parallel with

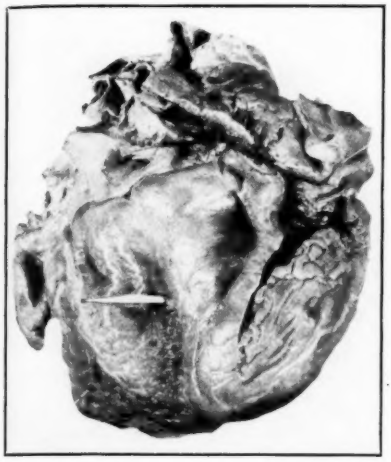

FIG. 1.—Case I showing rupture on posterior surface of left ventricle and surrounding pericarditis. The thrombosis of the descending coronary cannot be detected.

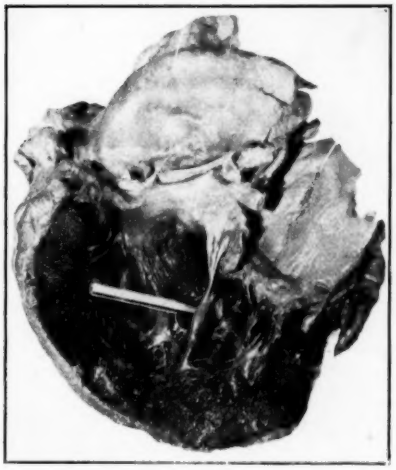

FIG. 2.—Case I showing oblique direction of tear with endocardial opening hidden behind the papillary muscle.

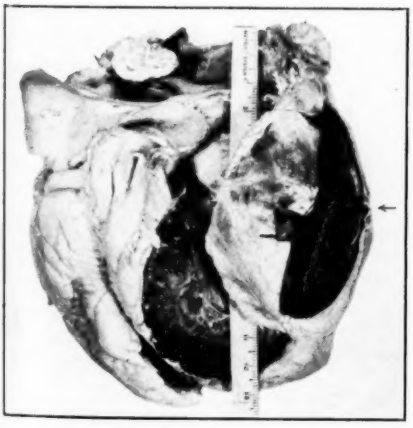

FIG. 3.—Case II with arrow pointing to line of rupture through wall of ventricle. Subepicardial hemorrhage is also shown.

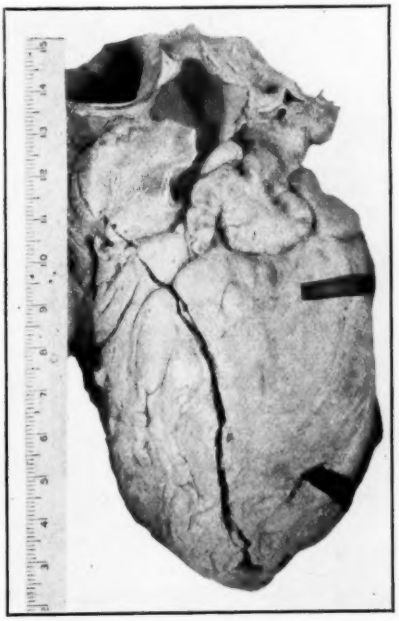

Fig. 4.—Case III, the ragged tear is seen joining the lower area from which section was taken.

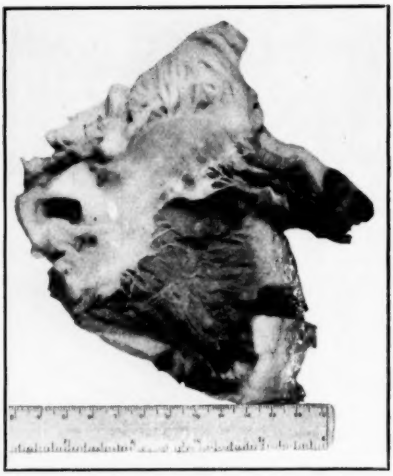

FIG. 5.—Case IV showing hemorrhagic infiltration and thinning of apex. Edge of the rupture is best seen in the tip of the reflected portion.

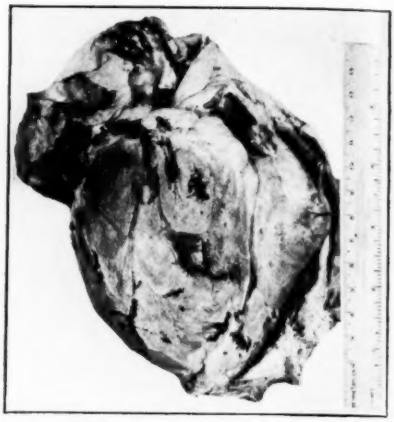

FIG. 6.—Case V showing transverse ragged tear 3 cm. in length, not penetrating into the cavity. Section has been taken in the middle of its upper border.

FIG. 7.—Case X showing the bulging hemorrhagic zone in left ventricle, from which various sections have been taken.

FIG. 8.—Case X, interior of left ventricle showing mural thrombus, subendocardial hemorrhage and great thinning of wall.

FIG. 9.—Case XII showing large, irregular "blow out" type of rupture.

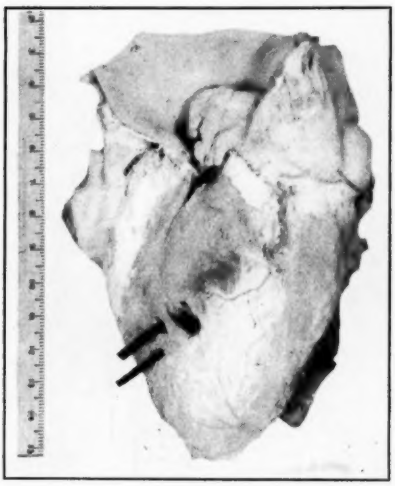

FIG. 10.—Case XVIII showing double rupture (with rods inserted) also place where section is taken. This specimen was fifty (50) years old at the time it was photographed.

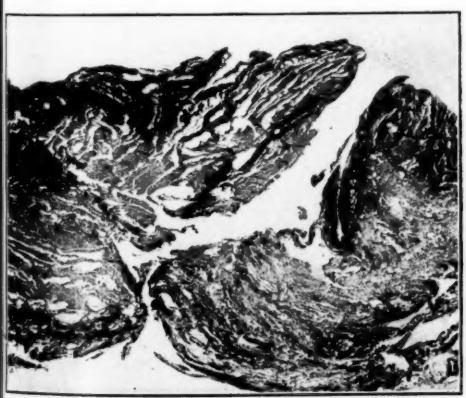

FIG. 11.—Photomicrograph of line of rupture of Case I.

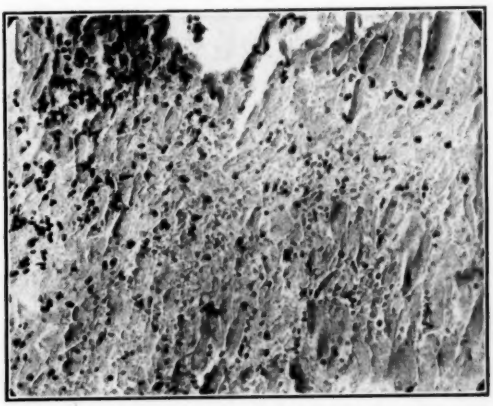

FIG. 12.—Photomicrograph of anemic infarct, following coronary thrombosis, with infiltration of red blood cells in the center of the picture and leukocytes at one edge. Case I.

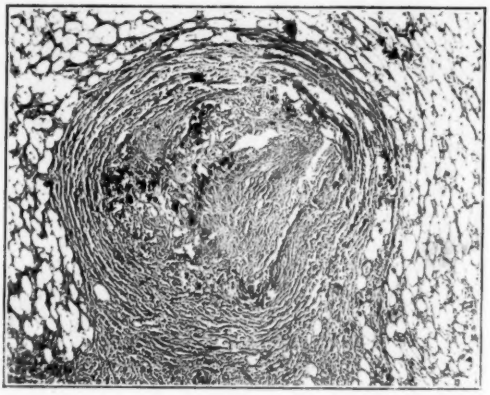

FIG. 13.—Photomicrograph of occluded branch of coronary artery. Case III.

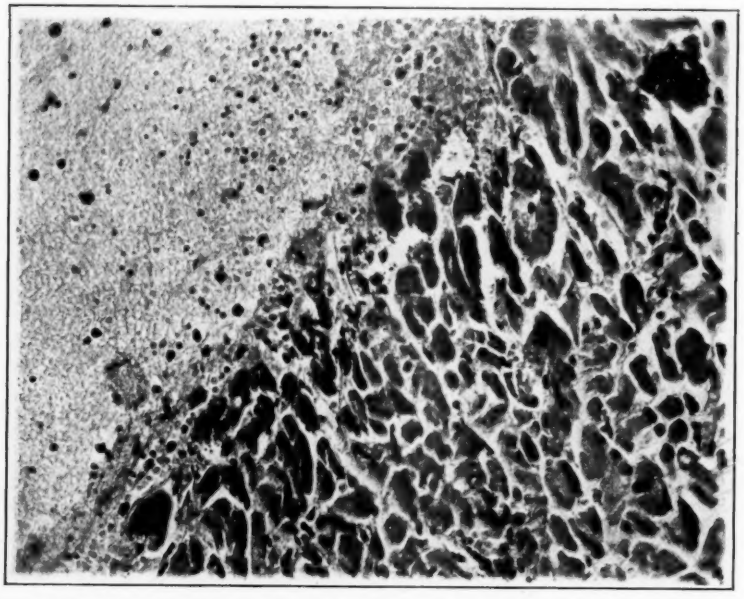

FIG. 14.—Photomicrograph of edge of rupture of Case III, showing hemosiderin granules in muscle cells along edge.

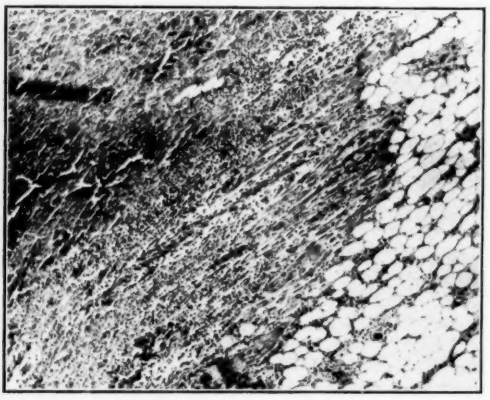

FIG. 15.—Photomicrograph of Case IV showing cellular infiltration in myocardium and epicardial fat and polyblastic connective tissue formation.

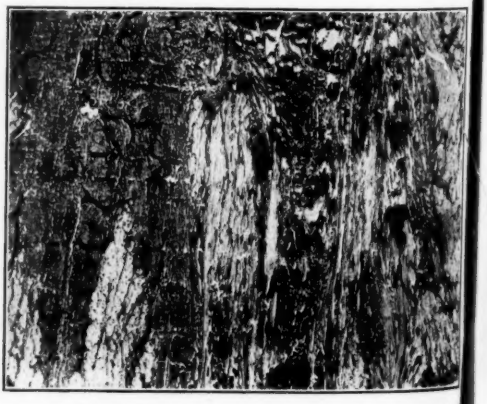

FIG. 16.—Photomicrograph of extensive myocardial fibrosis, Case XVIII.

the descending branch, with ragged edges discolored brown. Clotted blood was adherent and the muscle was friable. The wall of the left ventricle, which at the base was 2.3 cm. thick, measured 0.6 cm. at the apex, being thinned "almost to a membrane," and the cavity was dilated. It was a pale red color with yellowish spots especially toward the apex. Trabeculation was marked, though the muscle columns were flat and stretched. The tear was at the upper edge of the pouch and not at its thinnest point. The coronary arteries were sclerotic but the lumen was wide and partly filled with dark blood. No antemortem thrombus was found.

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle near dilated apex. Coronary sclerosis but no thrombosis.

Histology. There is a slight fleecy fibrosis between the fibers and, in patches, atrophy of muscle fibers with vacuolization and loss of longitudinal striæ. Areas of hemorrhage near the rupture vary with others of moderate round cell and polymorphonuclear infiltration. At the line of rupture the fibers are necrotic (wavy with total loss of nuclei and striæ). Many fibers terminate abruptly with ragged ends.

Histologic Diagnosis. Fibrosis and atrophy of myocardium. Necrosis and rupture of myocardium with hemorrhagic and cellular infiltration.

Comment. A good example of necrosis and rupture of the myocardium without coronary thrombosis. The coronary sclerosis was doubtless an important factor in the production both of the pouching and of the necrosis.

CASE XIII.—A man, aged seventy-four years, retired, complained of shortness of breath and said his stomach rebelled against certain foods. A minute after the doctor left him the patient died.

Autopsy. (P. B. B., No. 1541.) The pericardial cavity was full of blood clot, which entirely surrounded the heart. On the posterior side of the left ventricle was a raised area, 2 cm. in diameter, which was slightly bluish in spots and showed one slit, 13 mm. in length, through which a probe could be passed into the left ventricle. Above this was the appearance of a slit, 5 mm. in length, but there was no aperture. There was marked degeneration of the muscle of the ventricular wall, for a considerable distance on each side of the place of rupture. The coronary arteries showed a considerable degree of sclerosis and many places where the lumen was almost obliterated.

Anatomical Diagnosis. Rupture of left ventricle. Hemopericardium. Coronary sclerosis. Chronic myocarditis.

Histologic Diagnosis. Fatty degeneration. Necrosis and histolysis of the cardiac muscle.

Comment. Although the lumen of the coronary artery was not entirely obliterated, obstruction was sufficient to cause infarct and rupture.

CASE XIV.—A housewife, aged forty-two years, complained of pain in the back for two weeks. Her past history was negative. Four days before admission the pain radiated to the left arm. On the day before admission it was unusually sharp and lasted fifteen minutes. Physical examination showed a woman in much pain, rapid pulse and low blood pressure. She died after a week's stay in the hospital.

Autopsy. (P. B. B., No. 20104.) The pericardial cavity contained 250 cc. of bloody fluid and a large dark red blood clot almost surrounding the right auricle. Several clots were present in the apex region of the sac. The heart weighed 400 gm. On the anterior surface, in the wall of the left ventricle, was a rent, 3.5 cm. long, extending obliquely downward to the left, at the beginning about 1 cm. to the left of the anterior branch of the coronary artery. There was a thin delicate deposit of fibrin about this, surrounding it in a zone about 4 cm. in width. An incision in the

heart passing at right angles to this rent disclosed an actual defect in the wall as long as the linear lesion appearing on the surface, and about 4 mm. in width. There was here considerable loss of myocardial substance in the left ventricle, so that it was only 3 mm. in thickness in its greatest part. Filling this defect and about one-half of the ventricular space was a grayish-red thrombus, which had a relatively smooth surface. The remaining portion of the myocardium of the left ventricle measured 1.5 cm. in thickness, of a somewhat red cast with a few grayish-white lines, altogether suggesting fatty infiltration. The coronary arteries as a whole were markedly thickened, the right coronary showing great diminution of the lumen by calcification and atheromatous material concentrically arranged. Dissection of the left coronary showed much thickening of its wall along its entire length, and almost complete obliteration of the lumen of the main trunk. Histologically arteriosclerosis was rather generalized, but most marked in the artery where thrombosis occurred, with resulting infarction.

Anatomical Diagnosis. Rupture of the left ventricle of the heart, with thinning of its wall due to infarction. Hemopericardium. Thrombosis of the anterior descending branch of the left coronary artery.

Comment. Infarction due to the coronary sclerosis had probably existed for at least several days before the rupture occurred.

CASE XV.—A woman, aged sixty-three years, a practical nurse by occupation, had previously been at the hospital with diabetes and had frequent attacks of moderate dyspnea and palpitation with high blood pressure for many years. She came in the day before death, after having pain in the chest for six weeks, brought on by exertion. On the night before death she had severe pain beneath the sternum, radiating to the neck and shoulders.

Autopsy. (P. B. B., No. 21174.) The pericardial cavity contained 400 cc. of fluid which contained about 100 cc. of blood clot of recent formation. The fluid was thin and dark red. The heart weighed 400 gm. On the pericardial surface, about 4 cm. from the apex, in the region of the septum and the anterior descending branch of the left coronary artery, there was a slit about 3 cm. in length, through which blood oozed and around the margin of which there was discoloration for a distance of 8 mm. The slit was found to be 0.5 cm. from the septum and in the path of the above-mentioned coronary artery. There were also small adherent mural thrombi. This was undoubtedly the place of rupture and the coronary leading to this area was more contracted than the other coronaries and showed more sclerosis, the lumen being definitely smaller. No actual thrombi or emboli were found. The other coronaries were patent and distended.

Anatomical Diagnosis. Rupture of the heart with infarct of the left ventricle. Arteriosclerosis of the anterior branch of the left coronary artery. Hemopericardium.

Histology. Sections from the left ventricle show considerable areas of hemorrhage and blood clot in the myocardium. The muscle bundles are large and present several areas of scarring, also foci of fat between the muscle bundles. Many of the muscle fibers show parenchymatous degeneration. One of the sections shows in addition considerable numbers of polymorphonuclears and have infiltrated the myocardium. The appearance is that of acute and chronic myocarditis with rupture of heart.

Comment. Again sufficient coronary obstruction was present to cause infarction without actual obliteration. Duration of the infarct is problematical.

CASE XVI.—A man, aged seventy-two years, a cigar-maker, entered the hospital, February 26, 1925, complaining of pain in the chest. His family history was unimportant. For one year he had been troubled with nocturia, which had steadily become more annoying, so that for a few months he was forced to get up every half hour to urinate. For a few months he had complained of difficulty in starting urination, dribbling and burning micturition. Thirty-six years ago he had a chancre for which he received treatment with mercury, but subsequently a skin rash appeared which cleared on taking "black drops." In his present illness he had been dyspneic on slight exertion for several months. Occasionally he had been awakened at night with an attack of sharp substernal pain, which shot across the left side of his chest and down the ulnar surface of his left arm. These attacks occurred on exertion and sometimes made him feel an abnormal fear of death. Four days before entry, while sitting in a moving-picture house, he was seized with an attack much worse than any he had previously experienced. He went home and went to bed. The pain diminished considerably, but persisted in a milder degree until entry to the hospital. Except for frequency and dysuria, he was fairly comfortable until his fifth day in the hospital, when immediately after the use of a urinal he suddenly became pulseless, cyanotic and died almost immediately.

Autopsy. (P. B. B., No. 2537.) The pericardial cavity contained about 100 cc. of fluid blood as well as a large mass of blood clot lying between the two layers of pericardium. This clot weighed 420 gm. The heart was enlarged, weighing 500 gm., and was normal in shape. On the external surface and the posterior surface of the left ventricle, 1 cm. to the left of the intraventricular septum and about midway between the apex and the mitral valve, was a slitlike tear in the ventricular wall. This opening extended completely through the wall of the ventricle. On the external surface it was 2.5 cm. in length and 0.5 mm. in breadth, while on the inner surface it was about 1.5 cm. in length. The myocardium, radiating about the rupture for a distance of 2 to 3 cm., was mottled, deep red and reddish-gray, and here the tissue was apparently more friable than elsewhere in the ventricular wall. The gross appearance was that of infarction. The left coronary artery, from its point of origin down to its bifurcation, showed considerable arteriosclerotic thickening of its walls, and in some areas its walls were calcified. The anterior descending branch, at a point 1 cm. below its origin, had a very rigid calcified wall, and its lumen was so narrow that it barely admitted the sharp point of the scissors. The circumflex branch of the left coronary artery showed similar calcification of its wall, and at a point 1 cm. from its origin was a calcified plaque on which a considerable amount of adherent grayish-red, friable blood clot was seen.

Anatomical Diagnosis. Infarction of the heart with rupture through infarcted myocardium (posterior wall of the left ventricle). Hemopericardium. Coronary arteriosclerosis. Hypertrophy and dilatation of the heart.

Comment. Typical for this group.

Group IV. Coronary Sclerosis Only with Myocardial Fibrosis Only. CASE XVII.—M. M., a woman, aged seventy-six years, was brought by the police patrol to the Pennsylvania Hospital, April 23, 1914, with a clinical diagnosis of myocarditis. She had been sick for four days with epigastric and substernal pain, which at times had been severe. There was no history of dyspnea, edema, cyanosis or blood spitting. The heart sounds were weak and distant, but there were no murmurs. She arrived in "fair" condition, with some cough and pain in her left breast. An hour and a half later, before any further examination was made, she vomited slightly and suddenly stopped breathing.

Autopsy. (No. 1703, Dr. Bixby.) The pericardial cavity contained 500 cc. of fluid and clotted blood. On the anterior surface of the left ventricle, 1 cm. from the septum, and midway between the apex and base, was a linear opening, 15 mm. long, almost parallel to the septum, which communicated directly with the chamber of the left ventricle. On the external border were three irregular and quite superficial "cracks" in the pericardium. There was no sign of trauma. The heart weighed 270 gm., and had a moderate amount of superficial fat. The cavities were small. The muscle was very flabby and dark-red brown. "At the point of rupture the left ventricle measured only 1 cm." (presumably it measured considerably more at neighboring points). The internal opening was smaller than the external and partly covered by the papillary muscle. The right ventricle was also soft and flabby; the aortic valves slightly thickened. "The coronary vessels are somewhat harder than normal, and can be traced quite readily beneath the pericardium."

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle. Brown atrophy. Coronary and aortic sclerosis. Chronic passive congestion of lungs and spleen, fatty liver, chronic interstitial nephritis.

Histology. The pericardium contains much fat and a coronary vessel greatly thickened with connective tissue rich in cells. The muscle fibers are shrunken and wavy, but not fragmented or vacuolated. The cross striæ are not seen. The nuclei are large and well stained with considerable perinuclear pigment. The edge of the rupture is irregular with a thin layer of fibrin, and near the pericardium there is some infiltration with erythrocytes and leukocytes. There is considerable diffuse and focal infiltration of leukocytes, eosinophiles and lymphocytes. Some of the coronary arterioles are very thick walled, with almost obliterated lumen. Sections from the kidneys and liver showed several small collections of polymorphonuclears, and the spleen contained an unusual number of polymorphonuclears.

Histologic Diagnosis. Brown atrophy of the heart. Acute myocarditis. Splenitis, hepatitis and nephritis.

Comment. There is no evidence of coronary thrombosis or myocardial necrosis in this case, though the rupture seems to have been due to myocardial disease following coronary sclerosis. It is unfortunate that circumstances did not permit a more detailed study, so that the cause of the collections of polymorphonuclears and their relation, if any, to the rupture could be clarified. Their occurrence in organs other than the heart certainly suggests a pyemia which may have had an important connection with the rupture. The "cracks" in the pericardium are also of interest, even though their etiology and significance cannot be explained.

CASE XVIII.*—A woman, aged sixty-eight years, who had been in poor health for years, had a "fatty heart" for a year. The day of her death she felt much worse and vomited. Four hours later she felt so badly that she had to lie down; but in a few moments sat up, retched, threw herself back, and was dead.

Autopsy. The pericardial cavity contained 8 to 10 ounces of blood. On the anterior surface of the left ventricle, 2 inches from the apex and ½ inch from the septum were two openings $\frac{3}{16}$ and ⅛ inch long. On the internal surface one of these tears was hidden by a columna carnea. Grossly the heart did not seem fatty, but microscopically was said to be very fatty, the fibers breaking up longitudinally on slight violence. The aorta showed beginning sclerosis.

* This case was reported by Dr. W. W. Keen in the *Transactions of the Philadelphia Pathological Society*, 1874–1875, **5**, 94, but is included here as opportunity has since offered to make a histological study.

Further dissection, fifty years later, shows that the left coronary is greatly narrowed by a calcified area, 2 cm. from the aorta, before the descending branch is given off. It is also noted that the apex suddenly decreases from 1 cm. to about 3 mm. in thickness and is very fibrotic.

Histology. In spite of the great age of the material it is still possible to make out many histological details. For instance, near the apex the replacement of large areas of muscle fibers by dense bands of fibrous tissue, and in other areas definite perivascular fibrosis are easily made out. As striations and nuclei are not visible, it is impossible now to tell whether or not any acute necrosis was present. From its present appearance there does not seem to have been much fatty degeneration.

Diagnosis. Hemopericardium. Multiple rupture of the left ventricle. Coronary sclerosis with apical scar of old infarct.

Comment. This is a very good example of the kind of case which earlier passed as rupture due to fatty degeneration; but which in the light of later knowledge is found to have occurred in a heart that is the seat of marked coronary sclerosis with resultant thinning of the apex and replacement with scar tissue. Clearly coronary disease was an important factor in its causation.

Group V. Coronaries not Mentioned. CASE XIX.—E. K., an Irish woman, aged seventy-four years, was admitted to the hospital, July 15, 1902, with a clinical diagnosis of myocarditis, complaining of joint pains for ten years. She had had the usual diseases of childhood. The short history described a fat, white woman, with a full slow pulse, muffled heart sounds, but no audible murmurs. On July 26 she died suddenly.

Autopsy. (P. G. H., 5855, Dr. Coca.) The autopsy showed 300 cc. of blood in the pericardial cavity. The heart which weighed 400 gm. was pale and friable and had considerable epicardial fat. At the auriculoventricular junction on the anterior surface of the left ventricle was a tear, the walls of which were infiltrated with blood so as to form a swelling, 2 cm. in width, extending along the auriculoventricular groove. The mitral valves were fatty and sclerotic. The aorta showed moderate sclerosis, but the coronaries were not mentioned. There was no histologic report.

Anatomical Diagnosis. Fatty degeneration and rupture of left ventricle.

Comment. The paucity of evidence in this case makes it impossible to tell if this was really fatty degeneration or an infarction following occlusion of the left coronary.

CASE XX.—E. F., a white woman, aged sixty-four years, was admitted to the neurological service of Dr. Potts, September 14, 1901, with a hemiplegia of two years' standing. She was also aphasic and incontinent both of urine and feces. She also had a large ulcerating carcinoma of the breast and axilla. The only mention of the heart was that the second aortic sound was rough. The urine was negative. She died, December 5, 1902.

Autopsy. (P. G. H., 5981, Dr. F. P. Gay.) Autopsy showed a large well-nourished woman with the aforesaid cancer. The pericardial cavity was found full of blood, and the surface of the heart covered with fibrin. The apex was firmly adherent to the parietal pericardium by fibrous adhesions. When the fibrin was removed two ragged openings were found on the anterior surface extending through the copious fat into the cavity of the left ventricle. The coronaries were not mentioned. Histologically, there was much fragmentation and segmentation and perinuclear pigmentation, more marked in the right auricle than in the left ventricle. The diagnosis was made of brown atrophy.

Comment. As the section taken was obviously not from the neighborhood of the rupture, it is not possible to say what the condition of the

myocardium was at this point. The apical adhesion suggests an organized infarct, which in turn suggests coronary disease. The occurrence of further coronary occlusion with rupture of the resulting anemic infarct is at least as probable as any other explanation.

CASE XXI.—A clubman, aged sixty years, and a moderate drinker, came to the office of Dr. B. F. Stahl one morning about 8 A.M., complaining of precordial pain. Very little was known about his general condition, except that he said that he was seldom sick. After a short examination which revealed nothing startling, he was sent home, where he died suddenly in about an hour. There was loss of sphincter control just before death.

Autopsy. The pericardial cavity contained much blood, which was found to have come from several small tears in the lower third of the left ventricle, some of which communicated with its cavity. No further details of the condition of the heart are available.

Comment. None.

CASE XXII.—A. U., an aged female, died at the hospital, October 29, 1868, after having been insane nineteen years. She was a very large, fat, flabby woman, with a weak heart, some cough and dyspnea, but no edema. The day of her death she complained of pain in her left side. That evening she suddenly fell over, and died in a few minutes.

Autopsy. (P. G. H., 72.) The pericardial cavity contained 12 ounces of dark blood and clot. The heart was not much enlarged, weighing 14½ ounces, but was unusually flabby and covered with a fatty deposit. One inch from the apex of the anterior surface of the left ventricle, near the septum, was a tortuous irregular rent, ⅓ inch long on the endocardial surface and partly filled with firmly adherent clot. Its edges were rough and jagged and the external fibers seemed more torn than the internal. The coronary arteries were not mentioned.

Histology. Marked fatty degeneration of the muscle fibers either with central loss of transverse striæ or complete loss of striation with granular degeneration. Only a few healthy fibers remained.

Comment. This seems more like rupture due to fatty degeneration than any case of the series, and yet in the absence of more detailed statements, especially about the coronaries, the question must be left undecided.

Clinical and Pathologic Data. The figures for the age, sex and site of rupture and, to a lesser extent, for survival after rupture are based on all of the 654 cases. The remaining items are based almost entirely on the cases abstracted by us. It is perhaps unnecessary to add that the items that we have attempted to investigate were completely reported by very few and in most cases only a small number were mentioned.

CLINICAL. *Sex.* Three hundred and four were males and 217 were females. This corresponds fairly well with the generally accepted view that males are slightly more prone to the accident, though Quain stated that in his series the two sexes were equal in this respect. He gave no actual figures. The predominance of the causes of arteriosclerosis in the male sex is doubtless responsible. In statistics of coronary sclerosis the preponderance of males is more marked.

TABLE I.—SEX DISTRIBUTION.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
Male . .	185	Considered	38	81	304	58.3
Female .	112	Equal	37	68	217	41.7

Age. The average age at which rupture occurred was well in the sixties. The greatest number of cases occurred in this decade and the next greatest number in the seventies. When one considers how few persons relatively live to reach this age the results are truly astonishing. These figures confirm the opinion that spontaneous rupture of the heart is characteristically and strikingly a phenomenon of old age and suggest the fundamental importance of the condition of the coronaries. Particular interest attaches to the underlying cause of rupture in those patients who died young, and as one might expect, coronary disease no longer plays a predominant role. Of the 25 cases in our abstracted series under forty years there were 17 males to 8 females. Acute infection was a prominent factor in 9, lues in 5, trauma in 4, alcohol in 3, coronary disease in 2 and 3 doubtful. The auricles were more prominently involved; the left, 5 times; the right, 4; the right ventricle, 2; the left ventricle, 13; multiple tears, 2.

TABLE II.—AGE DISTRIBUTION.

Decennials.	Our analysis.		Quain.	Minet.	Robin.	Total.	Per cent.
Aged . . .	24		..	..	6	30	4.9
80+ . . .	12		6	13	21	52	8.6
70's . . .	63		24	22	58	167	27.7
60's . . .	99		33	19	37	188	31.3
50's . . .	47		13?	8	13	81	13.4
40's . . .	25		6?	4	8	43	7.1
30's . . .	12	25	3	2	6	23	3.9
20's . . .	4		2?	..	..	6	1.0
10's . . .	5		1?	2	..	8	1.4
1 to 10 . .	4		..	..	..	4	0.7
Total .	295		88	70	149	602	

Habits, Occupations and Predisposing Causes. Pertinent statements about these items were obtained in less than one-quarter of the cases abstracted by us. All social classes were subject to attack. Forty-seven of them were insane, a remarkably high incidence that has been noted by others and for which we have no explanation other than the common factor of arteriosclerosis. Except for this and the frequency of intemperate habits (noted in 24 cases), it cannot be said that these items of our study contributed much of interest or value. Even the notation of intemperance is subject to two general fallacies underlying statistics, namely, that a comparison with intemperance in subjects whose hearts did not rupture is not feasible and that possibly the authors' attentions may have been unduly focused on this point. Syphilis was conspicuous by

its rarity, except in those dying under forty years. Twelve were noted as obese, though this number should undoubtedly be much higher.

Exciting Causes. These are manifold in the coronary cases and vary from severe to the slightest form of exertion: Eating, 14 cases; walking, 13; defecation, 10; while conversing, 5; getting out of bed, 6; emotional excitement, 5; at toilet, 5; trauma, 3; convulsions, 3; attack of angina, 3; violent exertion, 2; sitting up in bed, dressing and so forth, 9. Five were, as far as they knew, perfectly well until they suddenly fell over dead. Twenty-one died during sleep (including 1 of our own series), but according to recent work of MacWilliams, this is not a period as free from strain as one might suppose. Particularly during dreams or restless sleep he found marked changes both in the rhythm of the heart (heart block, etc.) and in the blood pressure (increase of 20 to 30 mm.), which might easily be sufficient to rupture a necrotic myocardium.

Premonitory Symptoms. Attacks of vertigo, cough, dyspnea, syncope and even hematemesis are said to be indicative of the prodromal stages of rupture. They were not at all conspicuous in the case reports we studied and certainly not more so than would be found in the equal number of several cardiac cases whose hearts did not rupture. Diarrhea and vomiting seemed to have somewhat more significance. Anginal pain, on the other hand, was obviously important, being noted 70 times (in 7 out of 9 of the Boston cases), but this should be interpreted rather as a sign of coronary disease than of impending rupture. We know of no way accurately to differentiate the two conditions from the point of view of this symptom. In fact it may be said that the early symptoms are chiefly those of coronary disease and that it is still impossible to predict which cases of coronary disease are to suffer rupture. In a fair number of cases no preliminary symptoms preceded the acute attack.

Terminal Symptoms. Death is usually so sudden that in many cases the person is seen merely to fall over dead or is found dead. This applies to the auricular as well as to the ventricular cases. In a single case, where the physician chanced to be at the patient's bedside when the rupture occurred, a peculiar rushing, roaring sound was heard through the stethoscope that had been immediately placed over the patient's precordium. If life lasts a few moments there are signs of acute collapse, with air hunger, pallor or deep cyanosis, with stertorous breathing, cold sweat, perhaps vomiting, convulsions or unconsciousness, and in the few cases in which the heart has been ausculted the sounds are faint but rhythmic, or absent and the radial pulse imperceptible. In the rarer type lasting a few hours or more the patient may have the usual signs of acute cardiac failure, cough, angina or increasing signs of chronic heart failure. The time that the patient survived after the rup-

ture had taken place is given in Table III, as well as it can be estimated. But the reader must realize that this table is no certain picture of the facts. In several cases where death was reported as occurring so many days to weeks, and even, in 1 case, to over a month after rupture, consideration of the history and actual course of symptoms reported lead us to the decision that the time given for the first occurrence of rupture really indicated a situation arising from sudden occlusion of a coronary, while the actual rupture probably took place at a much later date. In these cases we have taken the liberty of tabulating the period of survival according to our own interpretation of the symptoms, rather than after the original report. At the present time, after more careful study of the histologic sections taken from our own cases, we feel that we have perhaps erred in these later interpretations of symptoms, and that some of these cases may really have survived longer than we thought possible. The wide infiltration of blood and leukocytes, and in some cases even an apparent attempt at connective tissue formation, are conditions that take more than a few minutes to produce.

TABLE III.

Survival.	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
"Sudden" . . .	178	71	31	8	288	72.0
Less than 10 min.	30	..	1	..	31	7.7
10 min. to 20 min.	7	..	1	..	8	2.0
20 min. to 1 hr.	3	..	..	..	3	0.8
1 hr. to 12 hrs. .	14	..	18	2	34	8.5
12 hrs. to 48 hrs. .	7	..	10	..	17	4.2
2 days to 8 days	3	..	10	..	13	3.3
8 days . . .	...	..	6	..	6	1.5
	242	71	77	10	400	

Mechanism of Death. This is still far from clear but probably varies with the size of the rupture and the consequent suddenness with which the pericardium is distended and the rest of the system deprived of its normal supply. For obvious reasons it is practically always impossible to make an accurate study in clinical cases. One might assume that cardiac arrest from the increasing pressure from the overdistended pericardium must play an important part, especially in the slow leaks that survive for some hours; but as Robin and Nicolle point out, some patients die with very little blood in the pericardium and cases of traumatic rupture are known to survive for a longer time than the spontaneous cases. On the other hand, Vance has recently shown in cases of traumatic rupture that if the escaped blood can drain into the pleural cavity death may be postponed for many hours. A second factor, especially in the sudden cases, is cerebral anemia, but to be so suddenly fatal the cerebrum must be deprived of more blood (perhaps by vasomotor action) than that lost into the pericardial cavity. The

terminal symptoms in some cases resemble those of fatal coronary thrombosis, where presumably cardiac arrest is primary; but others are more like those of cerebral syncope. Disturbance of cardiac mechanism, such as ventricular fibrillation, must also be taken into account.

PATHOLOGIC. *Site.* The site of the rupture was mentioned in almost every autopsy report. As will be seen in Table IV, the left ventricle greatly predominated and especially on its anterior surface. In Minet's and our series the anterior surface was involved 150 times as against 57 of the posterior, 38 of the apex and 5 of the external surface. Of 60 cases in which the location was further specified, the rupture was in the lower third in 35, in the middle third in 21 and the upper third in only 10. In traumatic cases, on the other hand, the left ventricle is less commonly involved than the right, on account of its less exposed position.

TABLE IV.—SITE OF RUPTURE.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
Right auricle	20	7	2	6	35	5.7
Left auricle	8	2	..	2	12	2.0
Right ventricle	32	13	5	13	63	10.2
Left ventricle	225	78	70	120	493	79.7
Miscellaneous	7	...	..	8	15	2.4
Totals	292	100	77	149	618	

The right ventricle is a poor second. Of the 32 cases of our series the anterior surface was involved 14 times (upper third, 1; middle third, 3; lower third, 6; not mentioned, 5); the lower third of the posterior surface, 2; the apex, 6; site unmentioned, 9.

The right auricle was ruptured 35 times (equally distributed over its various parts); the left only 12 times.

The 15 miscellaneous ruptures of the table were of the septum, apex (unqualified), or where the chamber was not designated. The reason for the predilection of the anterior surface of the left ventricle is chiefly that it is the descending branch of the left coronary that is most markedly atheromatous and most frequently thrombosed. The greater pressure in this chamber is undoubtedly an important contributing factor both to the rupture and to the greater amount of sclerosis. Discussion of the reason for the greater damage to the anterior coronary is hardly within the scope of this inquiry. As far as we know it has not been determined, but presumably the firmer support of the posterior surface by surrounding tissues would play a part.

It is noteworthy that the average age of those dying from rupture of an auricle was much less than that of the ventricular cases. In our series only 6 out of 25 cases of auricular rupture were over sixty years, with an average age of forty-three years, and in Robin and Nicolle's, 4 out of 10 with an average age of forty-seven years.

The non-coronary origin of the early deaths has already been discussed and of course the same factors apply here as well.

Character of Tear. In 223 cases in which the size of the rupture was given 60 (27 per cent) were less than 1 cm. in length, 5 of these were just large enough to admit a probe and 20 were less than 5 mm. in length. Sixty-four (28.7 per cent) were between 1 and 2 cm. in length; 43 (19.3 per cent), between 2 and 3 cm.; 24 (10.8 per cent), between 3 and 4 cm.; 17 (7.6 per cent), between 4 and 6 cm.; 15 (6.6 per cent), between 6 and 8 cm. The width (mentioned in 10 cases) varied from 2 to 25 mm., with an average of 8 mm. In 25 out of 36 cases the internal opening was given as smaller than the external; in 9 it was larger and in 2 equal.

The nature of the tear was mentioned in 166 cases and varied considerably. The edges were irregular or jagged in 72, clean cut in 20 and infiltrated with blood in 24. Linear tears were frequent, and described as oblique in 22, longitudinal in 18, transverse in 2, tortuous in 9, curved in 4, angular in 3, oval in 5, triradiate in 4, valvular in 1 and in 1 the apex had been pathologically amputated and lay free in the pericardial cavity.

The great majority (269) of cases were complete ruptures of a wall of the heart, producing large hemopericardia. In 8 of these, however, there was no mention of fluid blood or clot in the pericardial cavity. In 1 this was due to the rupture extending through an adherent diaphragm to the abdominal cavity. Presumably most of the others were the omissions of an incomplete report. Reports of partial ruptures were for the most part discarded. However, to get some idea of their usual position and cause, the first 16 cases met with were preserved. Of these, 4 were ruptured septa and 6 were papillary muscles. Of the other 6, 1 was a ruptured parasitic cyst (without blood in the pericardium); 1 showed separation of the auricular fibres without actual rupture (small amount of blood in pericardium); 1 ruptured into a coronary vein; 3 of varying depths from the pericardial surface did not reach the heart chamber (all showing blood in the pericardium).

Underlying Cause. The investigation of the cause underlying the rupture was considered by us to be one of the most important topics of the inquiry; but the incompleteness of many of the pathological reports has made it one of the least satisfactory. Thus, early impressed with the importance of the condition of the coronaries in this respect, we examined each report carefully for a statement about them, and yet in 156 out of 307 cases they are not mentioned—a fault by no means confined to the earlier observers. In fact even in the 22 cases now reported by us for the first time, in 4 it was impossible to get a statement about the coronaries. In Table V is given the results as best they can be tabulated, in the face of such difficulties. The largest group—fatty degeneration—is recruited chiefly from the older cases and undoubtedly contains

many—perhaps even a large majority—that today would be given different and more accurate designations.

TABLE V.—APPARENT EXCITING CAUSES.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
CONDITION OF CORONARIES GIVEN.						
Coronary thrombosis	74	6	51	24	145	23.8
Marked coronary disease with various myocardial lesions	68	1	..	44	113	18.5
Cause not determinable, coronaries approximately normal	9	..	..	2	11	1.8
CORONARIES NOT MENTIONED.						
Cause not determined	41	..	10	17	68	11.1
Heart apparently normal	4	..	..	1	5	0.8
Fatty degeneration and infiltration	59	77	15	35	186	30.4
Softening*	18	..	..	24	42	6.8
Thinned walls (aneurysm and fibrosis)	28	..	..	4	32	5.2
Syphilis	3	..	1	1	5	0.8
Tuberculosis	1	..	..	..	1	0.2
Parasitic cyst	1	..	..	1	2	0.4
Tumor (melanotic sarcoma)	1	..	..	..	1	0.2
					611	

Of the 154 cases of ruptured heart in which the condition of the coronaries is mentioned, they are said to be more or less diseased in all but 9. This would perhaps be expected where the average age is so high, but assumes a different and important aspect when coupled with the fact that in 74 cases actual thrombosis of the coronary had occurred and that in 32 more the coronary disease was sufficiently severe to cause either marked thinning of the ventricular wall (with or without aneurysmal dilatation, 20 cases) or acute or chronic myomalacia (organized infarct, 8 cases). Of the remaining 29 cases, coronary disease was associated with fatty degeneration in 12; sclerosis, brown atrophy and so forth, in 8; no other condition mentioned in 9.

In 157 cases the condition of the coronary arteries was not mentioned. In these cases also it was, of course, more difficult to appreciate the exact condition of the myocardium, on account of differences in terminology and conception of disease a generation ago. Thus "fatty degeneration" was a very popular term, which, based on gross inspection only, was probably frequently used incorrectly to describe acute infarction as well. In this group, for instance, it occurred 59 out of 157 times (37 per cent), while in the first group only 19 out of 151 times (12.6 per cent), 7 times associated with coronary thrombosis and 12 times with other forms of coronary disease. Continuing with the second

* This group includes indefinite descriptions such as apoplexy, red softening, ulceration, gelatinous, degeneration, etc. Doubtless many were really infarcts, others merely flabby or fatty and a few true abscesses.

group, "ulceration" was the assigned cause in 8 cases, and we suspect that this included some cases of infarct; infarct, as such, was given only 7 times. In 23 cases the ventricular wall was described as locally thinned to such a degree that it was obvious that the condition at least approximated cardiac aneurysm following coronary disease. Among the other assignable causes were fatty infiltration, 6 cases; fibrosis, 5 cases; syphilis, 3 cases; abscess, 3 cases; brown atrophy, 2 cases; parasitic cyst, tuberculosis, melanotic sarcoma, each 1 case. In 41 cases no cause was assignable, and in 4 the heart musculature was said to be normal. Without adequate histologic examination, however, this statement is of little value, and spontaneous rupture of a normal heart wall is properly questioned.

What a different picture these figures give from the usual textbook description of the underlying pathologic lesions of ruptured heart! Consideration of the two groups permits the conclusion that spontaneous rupture of the heart wall is due in the great majority of cases to antecedent coronary disease often with actual thrombosis, causing either an acute infarct (acute myomalacia) or organized infarct or such a poor state of nutrition that the muscle fibers degenerate and the thinned wall stretches to form a cardiac aneurysm. In the latter case rupture seems to occur either with or without a terminal necrosis of the muscle fibers. The small remaining minority is to be accounted for chiefly by acute and chronic infectious processes.

General Condition of the Heart. Apart from the condition of the myocardium at the site of the rupture, the most striking feature was the excessive amount of subpericardial fat, which was especially noted in 58 cases and was a prominent feature in most of the cases personally observed by us. It is noteworthy that the myocardial fibers were usually better preserved just beneath the pericardium than they were at other levels. So-called fatty degeneration was noted 34 times and the heart called pale and flabby (and often greasy), 25 times. Brown atrophy was noted 7 times; myocardial degeneration, 6; myocarditis, 4; fibrosis, 4. The heart was usually said to be enlarged. In 34 cases in which we have noted the weight, it averaged 433 gms. (270 to 870 gms. as extremes).

Discussion. It seems, then, that a person dies from a broken heart, not in young adult life from a great grief or emotion, but usually in old age, on account of diseased coronaries and from such immediate prosaic causes as walking, eating, defecation, slight exertion, or even during sleep. The condition was first described, as far as we can learn, by William Harvey, who also observed precordial pain in his patient and at autopsy found "An impediment to the passage of the blood from the left ventricle into the arteries." Morgagni (who himself died from it) described it in an old woman, aged seventy-five years, who had the traditional fatty heart.

Among its distinguished victims were George II (during defecation, Elleaume), Morgagni, the Scotch Dr. Abercrombie, Admiral Villeneuve, who after his defeat by the English was said to have committed suicide by lacerating the right auricle with a needle introduced between the ribs.

The underlying causative agents are reasonably well known, though it is far from clear why following coronary thrombosis, for instance, some infarcts should rupture and others go on to organization. The exciting causes also show a dissatisfying diversity that can only be partly accounted for by our inability to say exactly when the rupture occurred. One would naturally think that the accident would be especially associated with conditions causing increased intracardiac pressure; yet granted that this may occur at such unlikely times as during sleep, as has been previously suggested, still many other cases occurred after quite trivial movements or during absolute rest. Presumably the progress of the necrosis plays a more important part (compare our second case with liquefaction necrosis). Though apparently in some cases the functional weakness may be operative before the usual microscopic signs of necrosis are visible (Case X).

The actual method of production of the rupture is still open to discussion. Apparently some ruptures progress from the inside out and more *vice versa*, depending on which zone or layer the most necrotic and weakest focus happens to be in. From the postmortem appearances most are produced suddenly with rapid outpourings of blood (is this begun in systole or diastole?); but some, with sinuous, thrombin-covered walls, undoubtedly have progressed much more slowly.

The symptomatology is not characteristic and difficult to separate from that of coronary thrombosis, and the time available for study is usually very short. The diagnosis is therefore seldom made antemortem, and doubtless many cases of sudden death in the aged have had unsuspected ruptures. Terminal progressive increase of precordial dulness might in rare cases permit a correct diagnosis. In a few cases it has been made before autopsy, if not before death.

This is of no great matter, however, as the prognosis of a complete rupture is, as far as we know, invariably bad, and no method of treatment has been found to be of any use. It is, of course, possible that very tortuous minute passages might be blocked spontaneously by a clot long enough to permit organization or adhesion to the parietal pericardium to take place, and this possibility becomes more probable in the partial tears. As regards surgical intervention, in view of the diseased state of the myocardium, it is hardly conceivable that suture would be of any use, even if the correct diagnosis were made in sufficient time.

Study of the morbid anatomy brings out several interesting

moot points. The posthrombotic infarct, the organized thrombus, septic foci and so forth need not be further discussed here. The frequent concurrence of marked fatty deposit in the pericardium is curious, but its relation to the rupture obscure. The great diversity in the character of the tear and the variable relative size of the internal and external openings are indications that the mechanism of rupture differs in different cases, but offer no clue to solve this question. Another curious observation is that the internal opening has not infrequently been found partly hidden behind a papillary muscle, where it would seem to be relatively well protected. The case in which rupture occurred in an area supplied by a recently thrombosed artery, but not showing visible signs of necrosis (our Case X) indicates that functional weakness can be manifest before signs of structural change. It must be recognized also that coronary thrombosis may occur without signs or symptoms, that considerable myocardial necrosis may occur without coronary thrombosis (Cases XII–XVI) and that following coronary thrombosis the myocardium may at autopsy appear normal, even to the trained pathologist, and yet histologically show considerable necrotic and infiltrative changes (Case I).

Some of these question will undoubtedly be solved by future clinicopathologic observations; others can perhaps be better attacked by carefully planned animal experimentation.

Summary. From analysis of 22 cases hitherto unpublished, and 278 cases reported by others, and from a survey of 354 further cases from the literature (totaling 654), the following conclusions may be drawn:

Spontaneous rupture of the heart is chiefly an accident to the left ventricle of the aged; in the aged it is practically always due to coronary disease. It most frequently occurs in an acute infarct of the anterior surface of the left ventricle following sudden thrombosis of an artery or one of its branches; or less frequently the infarct may follow gradual fibrotic occlusion of the lumen.

With severe coronary sclerosis and consequent myocardial degeneration (usually with more or less cardiac aneurysm), rupture may occur in an area not obviously necrotic and supplied by a patent artery. The bursting of a cardiac aneurysm has been observed, but is rare. Evidence is presented to show that the formerly popular diagnosis of fatty degeneration is usually incorrect or open to serious question.

Other rarer causes of spontaneous rupture considered in this analysis are "ulceration," fatty infiltration, fibrosis, syphilis, abscess, brown atrophy, parasitic cyst, tuberculosis, melanotic sarcoma. Most of these are based on reports of little value on account of the antiquity or incompleteness of the data.

Evidence about the site and character of the tear is considerable and accurate, but the actual mechanism which produces rupture and the actual cause of death are not clearly understood.

All classes and occupations are liable and the exciting causes are most diverse. Premonitory symptoms are frequent but not characteristic. Terminal symptoms are usually so abrupt that little treatment can be even attempted and the antemortem diagnosis is seldom made.

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RELATION OF MORPHOLOGY TO THE PROGNOSIS OF AORTIC SYPHILIS.*

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Last year Scott reported a series of 25 cases of syphilitic disease of the aorta and of the aortic valves. The clinical picture was one of aortitis and aortic regurgitation, and the study was enhanced by the fact that autopsies were held on all of the cases, confirming the clinical findings. Several of the observations made by Scott are worthy of repetition. The cases presented the picture of aortic regurgitation with cardiac failure; the symptoms were not those usually associated with aortitis, such as substernal pain and nocturnal paroxysmal dyspnea; they lived for only a period of months after the onset of symptoms of cardiac failure, and the treatment seemed to be of little value. At autopsy it was noted that the aortitis merged into thickened, fibrosed, distorted aortic leaflets which produced an incompetent orifice and at times demonstrable narrowing or occlusion of the coronary openings was observed. These morphologic findings readily explain the serious prognosis in this group.

* Read before the Association of American Physicians at Washington, D. C., May 6, 1925.

We agree with Scott that the cases he has described represent a form of syphilis of the aorta and aortic valve commonly seen in hospital practice; moreover, it has been our experience, also, to see a rapid downward course in the majority of this type, although a few live from one to two years. We have never been impressed by the response they made to antisyphilitic treatment, although temporary relief of symptoms has followed the use of therapeutic measures, as Longcope noted some years ago. As this group represents a highly fatal form of aortic syphilis in a relatively short period of time, and as there appears to be among clinicians a growing tendency to regard this form as the only picture of the disease, we consider that some attention should be directed to other phases of the process in this location. There is another class of aortic syphilis which differs from that just mentioned, and which forms, in a way, a group showing some variations in its morphology, clinical features and in the response to treatment. The point of differentiation depends upon the fact that in more than half of the cases of aortitis observed at autopsy the aortic cusps are normal and the aortic orifice is intact. The development of a regurgitation may indicate a dilatation of the ring and not necessarily any valvular involvement. This holds true even when the aortitis has reached the stage of aneurysm development. Longcope has spoken of this in his excellent article on aortitis. The signs and symptoms are usually those of aortitis and not of cardiac failure. The duration of life is longer and it is our belief that antisyphilitic treatment is in some cases at least very effective in prolonging life. We wish to make a few remarks about this group, particularly with reference to one of the terminal manifestations of aortitis, namely, aneurysm. What pertains in general to the last stages of the process in the aortic wall in regard to prognosis would hold true for the earlier periods of the disease, but to a greater extent.

The morphologic pathology of the aorta is well known, particularly those changes which we believe to be due to syphilis, so it is not necessary to refer to it in any detail. One or two points, however, we desire to mention. The granulomatous process commences, as a rule, about 1½ inches above the aortic orifice and extends along the aortic wall to near the diaphragmatic opening. It may, but does not usually, go beyond. The lesion is frequently localized by almost abrupt lines at its beginning and end in the thoracic aorta. It is obvious that certain variations occur within these limits. It would seem that the ascending aorta is the most frequent and earliest part involved, and one would imagine that there should be a reason why the process does not spread down to the aortic valve, a distance of 1 to 2 inches, as readily as it reaches the more distant arch and descending thoracic portions. To be sure, the aortic valves are involved in a certain percentage. We believe it to be less than half. McCrae and Longcope have referred

to the dilatation of the aortic orifice, a condition which we regard as being more frequent than is generally considered. Klotz has suggested this peculiar distribution to be due to the fact that the spirochetæ reach the wall of the aorta by way of the lymphatics, and the first 1 to 2 inches of the aorta is not supplied by numerous lymphatics, as are the other portions where there is such abundant lymphoid tissue adjacent.

Microscopically in the wall of the aorta in aortitis or in aneurysm one sees varying stages of the granulomatous process as gummy necrosis on one hand and healed fibrosed lesions on the other. We would emphasize this latter point, namely, signs of spontaneous healing are evident. This process, moreover, may be so well developed as to very occasionally lead to a completely healed or latent aneurysm. True it is that such an end result is rare; but it is nevertheless an autopsy finding. Many museums have such specimens. Osler has spoken of the healing of some saccular aneurysms. Fibrous tissue is the principal element in this healing process. It is interesting in this connection to refer to what one might well term experimental aneurysm production from the work of C. C. Guthrie on the transplantation of segments of the wall of the inferior vena cava to the carotid artery in dogs, done a number of years ago. In one of these dogs he noticed that about a month after transplanting the piece of the wall of the inferior vena cava into the common carotid, an aneurysmal dilatation about the size and shape of an English walnut appeared and remained as such for the rest of the dog's life, which was eleven years. The animal during this time had two litters of pups, and was in several laboratory disturbances, so that one could freely say that the dog lived a normal life. Death was due to a hypernephroma with general metastases. Guthrie, Klotz and Permar reported the aneurysmal condition of the carotid, the wall of which was composed of fibrous tissue. Although the conditions here are not exactly the same as in the human aneurysm of syphilitic origin, in that inflammation is absent, yet the experiment does suggest that fibrous tissue is able to transplant the muscular wall of a large vessel and to assume its function quite readily. The same factor must be present in those cases of spontaneously healed or latent aneurysms of the aorta in the human, where it is very probable that the walls of the aorta are little more than fibrous tissue and that there is no active or progressive inflammatory reaction present. We are referring to this type of aneurysm not as an entity in the problem of prognosis on account of its rarity, but merely to indicate that fibrous tissue is capable of replacing the musculo-elastic wall of the aorta in a condition which has once been the site of an active inflammatory change. The development of a good fibrosis in the wall is the chief hope of prolonging life in aortitis with aneurysm.

An attempt to transfer this idea of healing by fibrosis with good

functional results to the clinical study of aneurysm of the aorta is another matter. Past experience would seem to point directly to failure, although prolongation of life is at times attained. In this connection the statistics of Boyd are of some interest in that the length of life of patients with aneurysm may extend over a considerable number of years. In 830 cases 20 per cent lived more than two years; 10 per cent over four years; 5 per cent over six years; 3 per cent over eight years and 2 per cent over ten years. It would appear that a regurgitant lesion at the aortic area, especially if due to involvement of the valves, tends toward a much shorter duration of life. In Scott's group it was nine months; but as this represents the average, there were undoubtedly some that lived considerably longer than this figure would indicate. Willius, in 167 cases of aortic regurgitation due to syphilis, found the duration of life to be fifteen months after their initial examination at the clinic. As the onset of symptoms in this type of aortic syphilis, as Scott has shown, is often very abrupt, these figures also fairly closely represent the duration after the appearance of the first clinical manifestations.

Several problems arise and some of them can only be solved by a large series of cases over a long period of time. The important and obvious point to be decided is the problem of dealing with the spirochetæ in the aortic wall. Can the organism be killed *in situ?* If this is possible the granulomatous inflammatory reaction will be replaced by fibrous tissue, or, in other words, healing will occur. It may be safer to assume that all we can hope to do would be to put the spirocheta into a latent state so that the inflammatory process does not progress. Under these conditions fibrosis might also develop, which would further protect the wall of the aorta. It is, moreover, likely that the older and more widely distributed lesion would offer much less change of a favorable response than the earlier or smaller process. Further, if the inflammatory process in the aorta is of the type which does not involve the aortic cusps, or has as yet produced no evidence of dilatation of the aortic orifice, the factor of regurgitation is not added and the possibility of a prolongation of life made much greater. The treatment employed must include the usual antisyphilitic measures and a prolonged rest. We have seen no ill effect from the careful use of arsphenamin or neoarsphenamin, but they are of much less value and may be even dangerous in those aneurysms having an aortic regurgitation. Certain aneurysms are, therefore, ruled out as not being suitable, because these cases are virtually the same as the group described by Scott; not a great deal can be done for them, although symptomatically improvement at times follows treatment.

We have had some experience with the medical treatment of aortic aneurysm and reported our findings in 3 cases five years ago chiefly because of the clinical improvement noticed. As 2 of these

cases are still living and in apparent good health it has seemed worth while to review some of the important points in their histories. One of the cases has been under our observation for almost nine years (eight years, ten months), the other about seven years (six years, ten months). The third case died about two and a half years after we first saw him, and it may be worth emphasizing that in his case a well-recognized aortic regurgitation with cardiac symptoms was associated with the aneurysm.

Case Reports. CASE I.—A man, aged thirty-six years, a molder, entered the Mercy Hospital in August, 1916, suffering from very severe choking attacks which occurred at night and were associated with considerable substernal pain. These symptoms had been present since June, 1916, or six weeks prior to his admission. He was perfectly well before that time. The attacks had become more frequent and the pain was more severe. Before his admission to the hospital they were occurring on three or four nights during the week. He had two attacks during the first week in the hospital, but these were the last. He had been working steadily at his trade, which was a fairly severe physical test, without any evidence of shortness of breath other than the attacks just described. In his past history there was very clear evidence of a primary sore fifteen years before the onset of the present symptoms.

The physical examination showed a very apparent pulsation in the first and second interspaces on the right and in the episternal notch, with a distinct lifting of the sternal end of the right clavicle with each pulsation. An expansile character was noted by palpation at this area. There was increased dulness to the right of the sternum above the level of the upper border of the third rib. On auscultation the heart sounds were regular, the aortic second was tympanitic and over the aortic area transmitted to the clavicle a systolic murmur was heard. There was no evidence of aortic regurgitation. By fluoroscopic examination an expansile pulsation in the aortic bulging was clearly seen. The plate showed an enlargement of the ascending aorta with a saccular-like bulging where it curved into the arch. The rest of the physical examination showed nothing of note. The Wassermann reaction was positive.

The following treatment was carried out: The patient was kept in bed for six weeks. During this time he was given daily inunctions of mercury (1 dram a day) and moderate-sized doses of potassium iodid (gr. 15, three times a day). After one week he was given six injections of arsphenamin in dosage of 0.2 gm. It was diluted to at least 100 cc. Following his discharge from the hospital he took one month of almost complete rest at home, and during the following month he had four injections of arsphenamin of the same amount, and this was the final number. He took mercury steadily for three years by the inunction method, resting two weeks in every two months. During the fourth and fifth year he was given mercury over a period of one month in every three. We have every reason to believe that he carried this out faithfully. At the end of three years his Wassermann was negative, and it was the same on the following year. During the winter of 1917 and the greater part of 1918 he was making 130 pound shells, and in the course of his work had to lift this weight from one hundred to one hundred and twenty times a day. The reason for this foolhardy procedure, because we had warned him against hard physical labor, was an economic one. Shellmaking was very remunerative work, particularly for a skilled workman. He, however, appeared to be none the worse for this test, but since then has done much lighter work. In 1919 he fell off

a ladder and broke one of his ribs, but he noticed no discomfort referable to the substernal area. The physical signs almost five years after showed the widening of the aorta, the systolic murmur and the tympanitic aortic second sound. The pulsations, however, were not visible on inspection. At this time, which was our last examination, he admitted that he felt as well as he had ever been, and he looked the part. For the past four years he has been living in California, but he has reported regularly every year by letter. He manages a garage, and according to his own recent statement he feels perfectly well and works every day. We have, therefore, not had the opportunity of examining him during this period.

CASE II.—A man, aged thirty-five years, laborer, entered the Mercy Hospital in July, 1918, suffering from intense substernal pain which forced him to sit up in bed or in a chair most of the night for several months. His symptoms dated back for a period well over a year. He complained also of some coughing, but the pain was the chief symptom. On physical examination the diagnosis was at once evident by inspection of the chest. There was a round swelling in the second right interspace just beyond the sternal border 4 cm. in diameter and protruding 2 cm. above the chest wall. This mass could be seen to pulsate and on palpation the expansile character was evident. There was a broad area of dulness on percussion and a systolic murmur was heard over this area. There was some question as to whether a diastolic murmur was evident at the aortic orifice. Our notes indicate "slight regurgitant aortic lesion," but the second sound is described as being ringing. McCrae has called attention to this in conditions of dilatation of the aorta and aortic ring. Later observations indicated no diastolic murmur. The Roentgen ray showed a very large aneurysm involving apparently most of the thoracic aorta. Under the fluoroscope it was expansile. The heart was not enlarged and its rhythm was regular and of good quality. The Wassermann was positive.

It appeared to us at first that treatment in this case could only be futile; but after two weeks in bed, under the usual iodid and daily mercury inunction, symptoms were considerably relieved and we decided to proceed with the other antisyphilitic therapy, arsphenamin. He remained in bed for the greater part of sixteen weeks, and during this time was given daily inunctions of mercury and ten intravenous injections of arsphenamin of 0.2 gm. and four of 0.3 gm. At the end of this time he left the hospital with instructions to take mercury by mouth and potassium iodid. We knew he would not carry out the inunctions at home. On leaving the hospital his symptoms had disappeared and the mass which had protruded from the chest was also gone, but one could still feel in the second right space the expansile pulsation.

This patient was very difficult to manage and extremely difficult to follow after he went home. He returned for examination in about fifteen months. He was feeling very well and was working. There was no indication of recurrence of the protrusion of the aneurysm. He had had no pain. Otherwise the signs were about the same. There was no aortic regurgitation. He had taken no further treatment after leaving the hospital.

We have seen him on two occasions since that time. In 1922, on examination, we found the physical signs to be about the same as when he was discharged. There was no regurgitation and the aneurysmal sac appeared to be about the same size. It was not evident on the surface at the side of the sternum. His Wassermann reaction was strongly positive. He told us that he was free from symptoms except for an occasional cough. Our last examination, a few weeks ago (1925), showed a very different picture. The sac of the aneurysm was again visible at the side of the

sternum, appearing as it was when he was first admitted to the hospital in 1918. Further, a very evident aortic regurgitation was noted and the heart was considerably enlarged. Coughing was the only symptom he complained of, although he apparently suffered at times from substernal discomfort. He had, however, been working steadily at a light occupation. With the exception of the treatment which he had while in the hospital, in 1918, it is probable that he had not taken mercury for more than two of three months during these years. We could not get him to coöperate.

CASE III.—A man, aged forty-two years, was admitted to the Mercy Hospital in August, 1918, suffering from nocturnal dyspnea and severe, almost constant, deep thoracic pain. In addition to this, on the slightest exertion he became very dyspneic. These symptoms had been present in some degree for a year and a half prior to his admission. There was no edema of the extremities, the liver was not palpable and the lungs were clear. Compensation appeared to be good. A diffuse throbbing pulsation over the whole upper chest and in the vessels of the neck was evident. Dulness was increased on both sides of the sternum above the cardiac area, particularly on the left side. A tracheal tug was present. There was a double murmur at the aortic area and some enlargement of the heart to the left. By Roentgen ray a large aneurysm involving the thoracic aorta was evident. The Wassermann reaction was positive. There was a history of a primary lesion twenty years previous to admission.

The patient rested in bed for a month, as he was unable on account of business responsibilities to take a longer rest. He was given potassium iodid and mercury in the usual manner, and he continued to take these drugs for about two and a half years. One month after beginning the inunctions he was given at weekly intervals six injections of arsphenamin, 0.2 gm., and after a period of one month three injections of 0.3 gm. at weekly intervals. This amount was repeated on the following month, so that in all he had twelve intravenous injections. He showed very marked improvement in that his symptoms were almost completely relieved, and during the first year and a half he put on 20 pounds in weight.

He worked steadily, managing his own hardware store, and reported on several occasions that he was feeling quite well. While waiting on a customer he fell over dead, which was about two and a half years after admission to the hospital. The suddenness of his death, in view of the coronary involvement that Scott has shown in his cases, would suggest that this was a possible explanation, although the sudden deaths due to myocardial changes described by Warthin must be remembered.

Discussion. There are certain points which these cases bring out, and they may, therefore, be briefly repeated: In the first the condition was recognized and treated very shortly after the onset of symptoms. The lesion was of the saccular type and had not developed to a large size. There was no clinical evidence that the process in the aorta had extended to the aortic orifice or to the valves, producing a regurgitation, and, therefore, the picture was never one of cardiac failure but of aortitis and aneurysm. If the antiluetic treatment in this patient has had any influence on the subsequent course of his disease, we believe the intensive and long use of mercury has been the most essential factor. He followed this faithfully for five years.

The second case illustrates a large aneurysm which, according to very definite symptoms, had existed for at least a year and a half prior to his appearance at the hospital. This aneurysm, therefore, has been present well over eight years. We are inclined to feel that the regurgitation at the aortic orifice in this instance is due to a dilatation of the ring. If we have accomplished anything in treatment it was done during the sixteen weeks he was in the hospital, for he has taken little or no treatment since that time. We would emphasize, also, the value of rest in bed. To prolong life over a few years in an aneurysm of this size should give some reason for hoping to do more for those seen earlier in their development. However, there are factors to be considered other than the actual size of the aneurysm, as the condition of the cardiac leaflets, coronary orifices and heart muscle, and its situation in the chest with reference to pressure on certain vital structures.

Our last case illustrates the type associated with aortic regurgitation, having clinical signs of cardiac failure and also of aortitis. This patient indicated the symptomatic relief which sometimes follows treatment even in advanced disease.

The prognosis in aortic syphilis has, therefore, some relation to the response to treatment, and the earlier the lesion is treated the better the result should be, although we frankly admit that it is a very difficult matter to be at all certain as to how much we have actually done by our therapy in the cases stated. Unfortunately, however, aortitis may, and probably does in the majority of cases, exist for a long period of time without producing any symptom which would lead the patient to his physician. Consequently an almost end result is presented even when the symptoms have been of short duration. This is true of the cardiac type that Scott describes and also of those forms which eventually develop aneurysm. Our first case illustrated this point very well, as his symptoms were present for only six weeks, although the process had undoubtedly been developing since his primary lesion fifteen years prior to that time. If this condition of aortitis is to be treated early its recognition by physical examination, serology and Roentgen ray must be far in advance of the onset of symptoms. More attention to the routine examination, especially of the aortic area, and routine serology are probably our best methods of approaching this problem of early diagnosis. Aortitis can be recognized by physical signs before any symptoms occur. These are well known, having been described in detail by McCrae.

Summary. 1. Syphilitic aortitis is most commonly localized in the thoracic portion of the aorta.

2. At times syphilitic aortitis is associated with aortic regurgitation, due to the process spreading from the aorta to the aortic ring or the aortic valves.

3. Syphilitic aortitis may be complicated by aneurysm formation. Some aneurysm cases are associated with an aortic regurgitation.

4. The occurrence of aortic regurgitation adds a grave factor to the prognosis of syphilitic aortitis.

5. Syphilitic aortitis, even to the stage of aneurysms, should be given specific treatment. Symptomatic relief nearly always follows, and it is possible that occasionally life may be prolonged for a considerable number of years in those cases where the process follows the usual morphologic distribution in the aorta, namely, noninvolvement of the valves, orifice or the first 1½ inch of the aorta.

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THE NEUROLOGICAL MECHANISM OF ANGINA PECTORIS AND ITS RELATION TO SURGICAL THERAPY.*

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In the surgical treatment of angina pectoris there has been surprising vagueness as to rational indications for the various operations employed. Ablations of different nerves and ganglia of the autonomic nervous system have been carried out, in some cases, with no apparent working hypothesis as to the relation of those nerves to the heart. The two cases reported below throw new light on this relation and make possible what would seem a more satisfactory explanation of the nervous mechanisms involved in angina pectoris.

The sympathetic nervous system has usually three direct connections with the cardiac plexus, the superior, middle and inferior cardiac nerves. All carry motor impulses to this plexus (Fig. 1). The superior cardiac nerve probably carries most or all of the constrictor fibers to the coronary vessels and aorta, as maintained by Ransom.[7] The middle and inferior cardiac nerves are called by Langley[9] the minor and major accelerators of the heart. Although

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all three nerves carry motor fibers, only the lower two contain sensory fibers from cardiac plexus to sympathetic ganglia (Fig. 2). These afferent impulses reach the central nervous system through

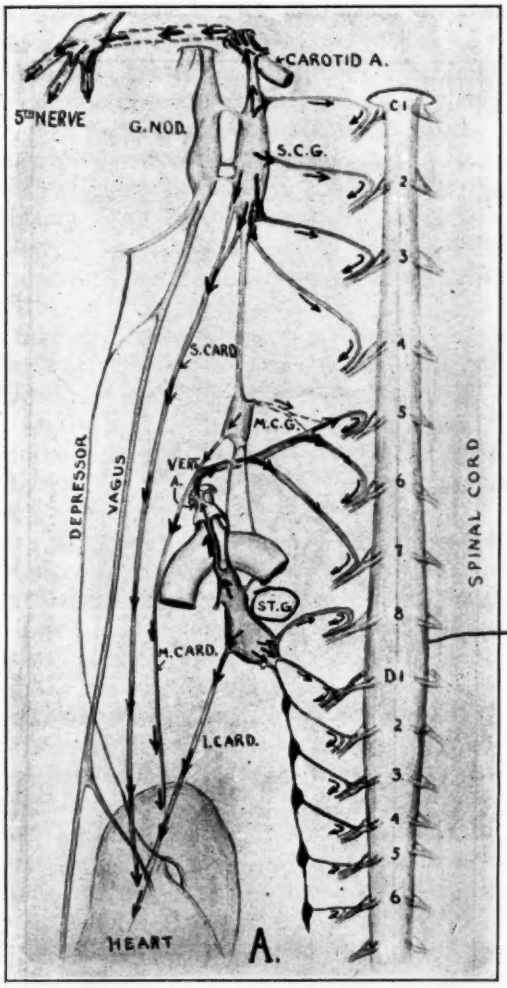

FIG. 1.—S. C. G., superior cervical ganglion of the sympathetic; M. C. G., middle cervical ganglion; St. G., stellate (inferior cervical and upper thoracic) ganglia; S. Card., M. Card., I. Card., superior, middle and inferior cardiac nerves; G, Nod., ganglion nodosum. Directions of motor discharges from sympathetic ganglia indicated by arrows. Gray rami accompany the spinal and trigeminal nerves without entering the central nervous system. An intermediate ganglion which is usually present is seen on the vertebral artery.

the rami communicantes to the upper six thoracic spinal segments (Fig. 2). It was shown by Langley[9] that stimulation of the superior cardiac or the cervical sympathetic trunk produced no reflexes in

animals when the connection between vagus and superior sympathetic ganglion was cut, whereas stimulation of the two lower cardiac nerves produced reflex response as long as there remained a pathway to the central nervous system along one of the six upper thoracic rami communicantes. Dogiel showed there were sensory

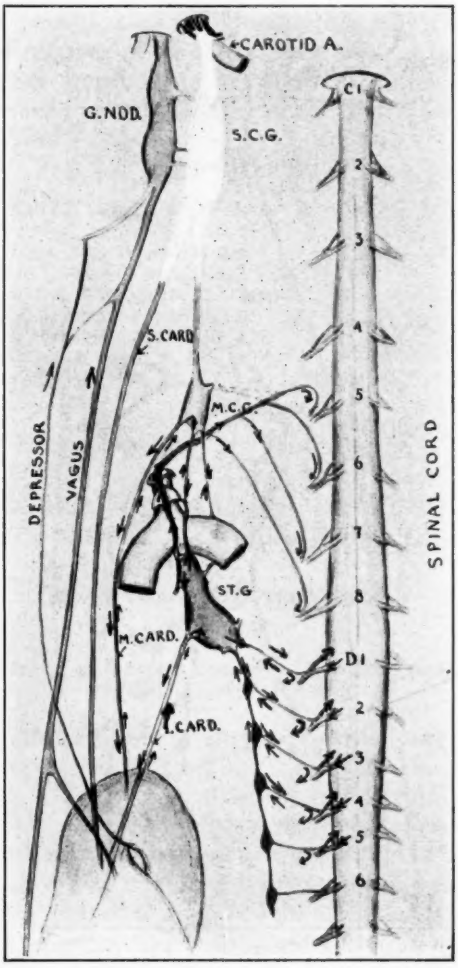

FIG. 2.—Arrows indicate direction of afferent impulses from cardiac plexus to central nervous system.

as well as motor endings in bloodvessels, although that does not mean that these fibers are true pain conductors. He pointed out that these sensory fibers[3] were provided with thin myelinated sheaths and Edgeworth[7] found that histologically fibers of this type all pass up into the central nervous system by way of the rami com-

municantes of the upper thoracic segments and by the vagus, an observation verified by Ransom. Thus there is good physiological and histological evidence to show that the afferent paths from heart to central nervous system pass by way of the middle and inferior cardiac nerves and the vagus; also, that the superior sympathetic ganglion is not a station in this path.

In the light of these anatomical findings, the rationale (or lack of it) for the various operations performed appears evident. Jonnesco[8] removed the lower part or all of the chain in order to eliminate all afferent paths through the sympathetic. Hoffer[6] cut a branch of the vagus which he believed to be the depressor, to eliminate vagus afferents, and Coffey and Brown[1] removed the superior sympathetic ganglion because it was easily accessible. Ransom has suggested that this last operation may prevent reflex spasm in the coronaries and aorta.

As I shall take up the following cases only from a neurological point of view, it is sufficient to say that the first patient, G. C., had a syphilitic aortitis with aortic insufficiency. The angina pectoris was severe and completely incapacitating. It began in the manubrium and spread to the inner aspect of the left arm. If not checked by nitroglycerin, it then spread to the inner aspect of the right arm.

According to the theory of referred pain, as first suggested by Head[5] and Mackenzie,[11] a stimulus passes from the heart via the sympathetic to a posterior root ganglion. Here, in some way the sympathetic impulse is turned into stimulation of certain spinal ganglion cells which cause the patient to feel pain. This pain he seems to feel in the sensory distribution of the nerve root in question. It is therefore called referred pain. On the basis of this theory, it should have been sufficient to remove the middle and inferior cervical and stellate ganglia on both sides. This of course interrupts all sympathetic connection between cardiac plexus and central nervous system. Consequently, this was done on both sides at the same operation, leaving in place both superior cervical ganglia. It is evident that each superior sympathetic ganglion is now isolated (Fig. 3). Its only connection with the spinal cord which had been by means of the sympathetic chain has now been removed. The superior ganglion is provided only with efferent outlets to the vessels of the brain, the outgoing branches of the fifth nerve, the peripheral distribution of the highest three or four cervical spinal nerves and the cardiac plexus. It cannot be the path for sensory conduction because, first, there are apparently no sensory fibers in the superior cardiac nerve and secondly, because the ganglion now has no known connection with the central nervous system.

Nevertheless, on the ninth day after operation the patient sent for the intern on the ward because of pain in his head and the following is Dr. Samuel Lambert's careful note made at the time:

"The patient was sitting straight up in bed. His forehead was moist with perspiration equally on both sides. The rest of his body was warm but not moist. He was perfectly clear mentally. He said he had a dull pain which started all around his neck, just below his

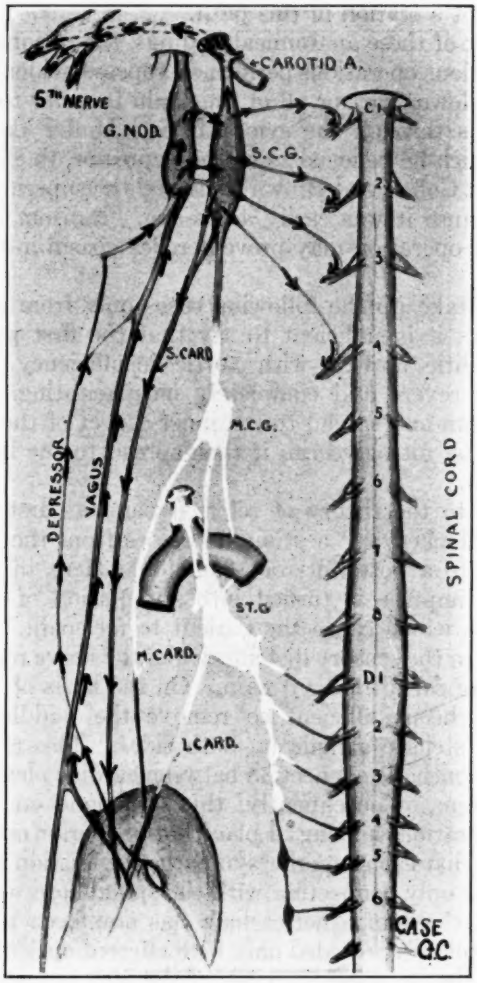

FIG. 3.—Case G. C., middle and inferior cervical and upper thoracic ganglia removed. Arrows indicate direction of impulses in remaining fibers of autonomic system.

jaw, like a collar. It went up into his gums and then up the sides of his head to the top. At the same time he had a feeling of tightness in exactly the same locations. He had no pain or feeling of constriction any other place. His blood pressure was over 300 (systolic) and 0 (diastolic). He felt a little nauseated momentarily.

"He was given 0.0006 gm. nitroglycerin. After five minutes he said the pain had entirely left. In the patient's words, 'It just kind of floated away.' His blood pressure was still 300 (systolic and 0 (diastolic).

"Fifteen minutes later he said he had a very slight pain returning in his lower jaw. The blood pressure was still 300+ and 0. There was no perspiration on his forehead. The pulse throughout 82 to 86.

"One-half hour later he was given a second dose of nitroglycerin and the pain was completely gone. The blood pressure was 170 (systolic) and 0 (diastolic)."

It is now a little over a year since the operation and although he was restored to activity again, he has continued to have attacks of angina pectoris in the face, head and sometimes neck. These attacks are easily relieved by nitroglycerin.

It is impossible to explain these seizures on the basis of referred pain. The angina which the patient experienced was in the distribution of the fibers of the superior sympathetic ganglion which accompany the branches of the fifth nerve and upper three cervical nerves, but this ganglion is cut off from the central nervous system. Therefore, I have assumed that the ganglion is stimulated by a reflex in the autonomic system.

Similar reflexes have been described in the sympathetic nervous system elsewhere, and called by Langley and Anderson[10] axone reflexes (Sokownin reflexes). Simply expressed, they may be described as follows: Axones (in the lumbosacral autonomic) as they pass on down a nerve, such as the hypogastric, send off connector fibers to numerous cells in the adjacent sympathetic ganglion. Stimulation of the axone below awakens to action the motor cells in the ganglion which receive connectors from that axone. Thus if the inferior mesenteric ganglia be isolated from the central nervous system and the right hypogastric nerve be cut and its upper segment stimulated there results blanching of the bladder and rectum on the other side. These long axones which give rise to axone reflexes were shown to have their nerve cells in the central nervous system. Gaskell, in his masterly book on "The Involuntary Nervous System," after discussing these splanchnic reflexes, says, "There is no reason to suppose that one part of the involuntary nervous system differs in essentials from another. I imagine, therefore, that the cranial connector fibers in the vagus nerve . . . also send off collaterals so as to connect with more than one motor nerve cell; that therefore, when the organs supplied by such motor cells are isolated from the central nervous system, reflexes can take place in them which are also of the nature of axone reflexes."

Therefore, in the opinion of Gaskell, it would not be contrary to what is known of the physiology of the involuntary nervous system to suppose the vagus may enter into an axone reflex. If one assumes that stimulation passes from the irritable area in the heart or

aorta by way of the vagus or depressor nerve, it would then be transmitted by connector fibers through the abundant anastomosis from the ganglion nodosum to the ganglion cells of the superior sympathetic. These motor cells being stimulated would cause spasm in the bloodvessels innervated by that outflow, that is, the coronary arteries, the vessels of the head, face and neck. Their activity would likewise cause sweating in the same peripheral area (and this was the case), and the constriction of the vessels might perhaps be expected to raise the blood pressure still higher, a condition which also was found true.

If it is the actual peripheral arterial spasm that is responsible for the sensation, the use of a drug which relaxes the smooth muscle of these contracting vessels should abolish the pain, independent of the drug's action on the heart. Of course the specific physiological action of nitrites is to relax smooth muscle. It may be thus that it relieves angina pectoris.

I have used the word pain to describe the sensation of angina, but this patient, like many others, describes it as a pressure or great weight, something like a terrible constriction. This characterized the sensation as felt formerly in the precordium and arms and, since the operation, in the face.

If the immediate cause of the angina is peripheral vessel spasm, this spasm must be felt directly by the patient, through the same cerebrospinal paths used for the conduction of ordinary types of pain, as is the case in certain other sympathetic reflexes to be mentioned below.

The second patient to be described S. A., aged thirty-eight years, had a general arteriosclerosis and hypertension, his blood pressure averaging about 210/105. Walking across the ward was sufficient exertion to precipitate a severe attack of angina pectoris, felt as pressure in the precordium and left arm.

I removed the left cervical sympathetic chain, including all the cervical ganglia and the stellate ganglion, on the advice of Dr. Levy. When the patient became active after the operation, typical attacks of angina pectoris reappeared. But now it was on the right side and the sweating which accompanied it was on the right side of the face and right arm. Some pressure was felt in the upper sternum, right side of the neck and inner aspect of the right arm. These attacks continued and he was again operated upon. This time, because of the good results reported by Coffey and Brown, the simple operation of removing the superior sympathetic ganglion was performed. On the third day after removal of the right superior ganglion, angina recurred. Now the pain appeared to be in the right arm, the right neck being left out, and sweating now during attacks was altogether absent in the face but appeared in the right arm and chest.

Thus a third time we see that the angina was felt in the area where

the sympathetic motor supply was intact. After the second operation the patient's systolic pressure fell from an average of 210 to 170. It rose, however, as was the case with the first patient, during attacks (reaching 205). Recovery from the immediate effects of the operation was satisfactory, but on the eighth day after operation the

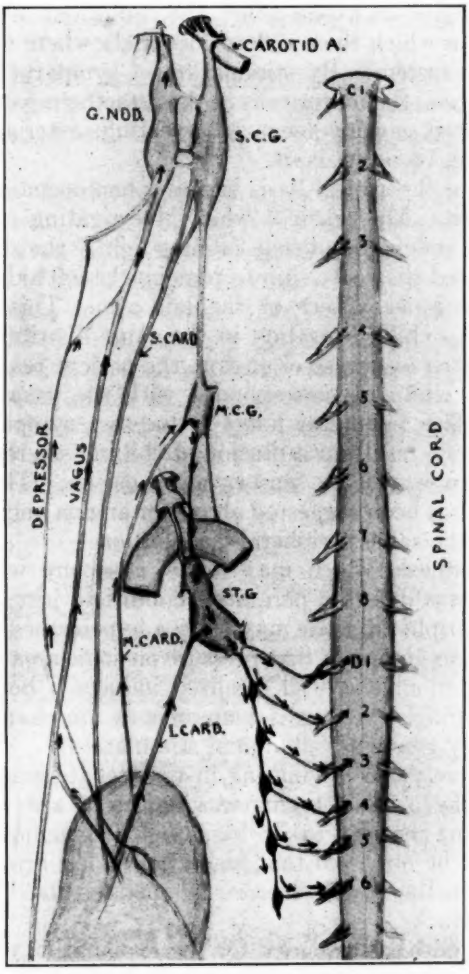

FIG. 4.—Case S. A. (right side). Superior sympathetic ganglion has been removed. Arrows indicate direction of impulses in remaining fibers.

patient suddenly had what Dr. Levy thought was a coronary occlusion, and he died on the sixteenth day.

As seen in Fig. 4, the second patient presented on the right side a condition the reverse of that which obtained in the first patient. The mechanism is present for a possible explanation of the angina

on the basis of Head's theory of referred pain. That is, there are present afferent paths from cardiac plexus to the upper thoracic spinal cord. On the other hand, before the superior ganglion was removed, some of the discomfort was felt in the right neck, an area supplied with motor fibers from this ganglion. After the removal this pain was not felt.

On the theory of an axone reflex, the conditions are exactly the same as those in which these reflexes occur elsewhere in the sympathetic nervous system. By stimulation of sympathetic axones in the cardiac plexus, the motor cells in the intact sympathetic ganglia would be excited causing localized sweating, arterial spasm and some increase in blood pressure.

On the above theoretical basis certain phenomena of angina are easily explained. Mackenzie,[12] when investigating the pilomotor (or goose skin) reflex, found that rubbing lightly the skin under the left breast caused the goose skin to pass up the left side of the chest and down the inner aspect of the left arm. This sympathetic reflex induced a chilly sensation in the same distribution. When he tried the reflex on a case of angina, the patient remarked in surprise that the chilliness corresponded with the usual distribution of his pain. This pilomotor reflex is due to a sympathetic motor discharge and the resultant sensation of chilliness is reported to the consciousness by way of the sensory spinal nerves. The mechanism is the same as has been suggested above for angina and the resulting sensation has the same peripheral distribution.

The hyperesthesia which may follow a seizure would indicate that the pain was due to a peripheral condition, just as any severe pain from a peripheral cause may leave a hyperesthesia of the skin. Patients at times complain that pressure on some area of skin which may be quite small and well localized induces a bout of angina. Such pressure might perhaps set up smooth muscle contraction in an area already receiving subliminal stimulation.

That an angiospasm originating in the stellate ganglion may be the cause of the pain in angina was suggested also by Brünning[2] for the following reasons: (*a*) In handling the ganglion preparatory to removing it he observed that his patient's left arm became suddenly blue as in Raynaud's disease; (*b*) the fact that blood pressure rises during attacks.

The new hypothesis proposed for the explanation of the nervous mechanism in angina pectoris depends upon an autonomic reflex. It might well be called, therefore, *reflex pain*. It causes peripheral spasm of smooth muscle and thus may resemble the pain in various angiospastic conditions. It differs from the referred pain of Head principally in that the point of contact of sympathetic and cerebrospinal system is shifted from the posterior root to the periphery where there are other analogous contacts between the two systems. No attempt is made in this communication to expand the hypothesis

to other types of visceral pain nor to analyze different kinds of cardiac pain.

Conclusions. The following practical conclusions may be drawn:

1. The removal of a sympathetic ganglion removes the possibility of angina pectoris in the *motor* distribution of that ganglion only.

2. Pain is still possible in the motor distribution of the remaining ganglia, provided the stimulus arising in the heart or aorta is adequate.

3. Success in the operation depends not upon interrupting a direct afferent path from cardiac plexus to central nervous system as has been assumed, but upon the interruption of autonomic reflexes.

4. Complete cervico-upper-thoracic sympathectomy abolishes the pain, but should only be employed in cases where life is really insupportable even under the best medical care.

5. Removal of the superior cervical sympathetic ganglion does not render angina in the motor distribution of the other ganglia impossible. Its removal can only be justified on the basis of some resultant alteration in the coronary vessels or aorta which are innervated by it through the superior cardiac nerve.

6. Even if the operation is successful in abolishing pain, the patient should not be called cured but should still be considered as having a serious cardiac disease, and be treated accordingly.

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LIPIODOL IN NEUROSURGERY.

With a Report of a Case with Deleterious Results.

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Ever since neurosurgery has entered into its important sphere as a specialized entity, neurosurgeons as well as neurologists have been seeking to overcome the errors encountered in false spinal localization, especially in reference to the diagnosis of spinal cord tumors, and have been searching for some method whereby the exact level of cord obstruction could be accurately determined. It is not an unusual occurrence for neurosurgeons to explore a vertebral canal at a site much lower than where the true lesion actually is located.

The best indicator at our command at the present time for disclosing a level lesion is a careful and thorough neurologic examination; but even the best present-day study is at times not sufficiently accurate. The Ayer[1] test is of inestimable value in the differential diagnosis of spinal subarachnoid occlusion, and yet it lacks the all-essential and much-desired faculty of localization. The Queckenstedt[2] test also is not infallible in its results: In cases of incomplete or partial spinal obstruction the interpretation of the findings obtained from this procedure often leaves us in a dilemma. I personally have always regarded this test merely in the light of a confirmatory observation and have not considered it as a decisive indication; nor have I permitted normal readings to sway me from the diagnosis of cord compression when the neurologic findings indicated such a lesion. The same objection can be raised to this sign as to the Ayer test, namely, it fails to localize the segment. Dandy's[3] method of introducing air into the spinal canal appears to be the nearest approach to a satisfactory solution of the problem, aside from being entirely harmless. In the cervical region one is apt to become confused with the air in the trachea, but in the other regions of the vertebral canal the level of air is more distinct and less apt to cause confusion.

In 1921 Sicard and Forestier[4] first reported the value of lipiodol as a means of determining the absolute localization of spinal subarachnoid blockage. Lipiodol is a 54 per cent solution of metallic iodin in a vegetable oil. This substance is introduced into the vertebral canal by way of a puncture of the cisterna magna and the oil permitted to gravitate down to the site of the spinal obstruction where it remains impinged. A Roentgen ray photograph is then taken to reveal the opaque substance at the exact site of occlusion. In October, 1923, Sicard, Paraf and Laplane[5] reported the

intraspinal use of lipiodol in 150 cases, of which 50 were given by the way of the cisternal route, without any fatalities. The impression gained from these authors is that this material is a perfectly harmless and innocent solution, in spite of the fact that it is almost nonabsorbable and has remained *in situ* for over two years in some of their cases. Sargent[6] has corroborated the visualizing and localizing value of this preparation in 3 cases which at operation revealed three spinal cord tumors.

Ayer and Mixter,[7] experimenting with iodipin,* a less irritating preparation, and also with an iodin preparation of the same percentage as the original French product, found that the six cats employed in their work displayed evidences of meningeal irritation. The cell count in the spinal fluid of 1 case was 2700 cells per c.mm. the day after the injection of the oily preparation and 4420 in another case on the third day after the injection. One cat died of convulsions. These workers next injected iodipin into the subarachnoid spaces of 2 patients, and they felt that in 1 case a reaction was displayed by an otherwise unexplained rise in temperature for one week. They concluded that the oily substance (iodipin) was distinctly irritating and its use should be greatly restricted and guarded.

My experience with lipiodol has been limited to 3 cases, 2 of which I have not been able to follow up and the other case, the cause of this report, has demonstrated to me unequivocal and undoubted evidence of the irritative power of this substance.

Case History. Mr. V. L. (N. Y. P. H., No. 4914), aged thirty-seven years, married, white, laborer, born in Finland, was admitted for the first time on May 5, 1924. The patient entered the hospital with the complaint of difficulty in locomotion for the past two and one-half years.

About four and one-half years previously the patient first noticed that his left leg felt numb and that it soon became anesthetic to both heat and cold. This was readily noted on immersing the lower extremities into water and has persisted up to the present. His right leg remained normal. Two years later weakness in the right knee occurred with a slight limp on that side. After an interval of six months he began to drag the right foot. One year later involvement of the left leg began with stiffness. Both legs have grown progressively worse and have increasingly incapacitated him in his locomotion. The legs are easily fatigued by walking, which is not felt when he is either sitting or reclining. At no time during the course of his entire illness were there any symptoms referable to the involvement of the rectal or vesical sphincters. Venereal diseases were emphatically denied.

* Iodipin, 40 per cent solution of iodin in a vegetable oil, prepared by Merck & Co.

At the age of eighteen years the patient, while employed as a seaman, fell 15 feet into the hold of a ship. He was unconscious for two weeks. At this time he sustained a cranial as well as a vertebral injury. He was discharged from the hospital in three months without any residual paralysis.

Physical Examination. The gait was that of a typical spastic paraplegic; all associated movements were normally present. A slight Romberg sign was noted. There was also a fine rapid tremor of the hands. Ataxia and adiadochokinesis of the upper extremities were absent. The motor system indicated definite and severe involvement. The deep reflexes of the upper extremities, such as the biceps and triceps, were equally active; the patella reflexes were equally markedly exaggerated; percussion of the tendo Achilles produced transient clonus on both sides; persistent and permanent clonus was elicited at both tendo Achilles; double Babinski and double Chaddock signs were obtained. The four superficial abdominal reflexes were all absent; the cremasterics on the other hand were both normally present.

The cranial nerves were practically negative. The right fundus showed a distinct pallor of the temporal rim of the disc; on the left side the physiologic cup was very distinct, and there was less suspicion of a temporal pallor, although there seemed to be some slight indication of the same. The pupils were equal and reacted to light; accommodation and consensual reflexes. The extraocular movements were normal. A slight bilateral nystagmus was observed which was more marked on looking to the right and became less on persistently looking to the same side. The corneal reflexes were active and the sensory as well as the motor supply of the trigeminal nerves were normal. The facial reflexes on both sides were intact. The Rinne's tests were positive; the Weber test on the right side responded normally; on the left the test was not correctly interpreted; the greater intensity was referred to the opposite ear on one occasion and of equal intensity in both ears on another occasion. The uvula pointed in the center and moved properly; the pharyngeal reflex was active; the tongue protruded in the center; the movements were normal and no tremor was observed.

The sensory examination revealed a definite level of disturbance in all four tests. To cotton (touch) there was an area of anesthesia extending from the distribution of the fourth lumbar segment to and including the fifth sacral segment on the left side; from the level of the eighth dorsal segment to the fourth lumbar on the same side hypesthesia was present. The right side presented no abnormalities. On testing for pain it was found that hypalgesia extended from the ninth thoracic level down on the left side. The right was again uninvolved. Hot and cold sensations gave the same results, namely, thermoanesthesia from the twelfth dorsal segment down and hypthermoanesthesia from the ninth to the twelfth dorsal

distributions. As with the other tests, the left side alone was affected.

The general physical examination was negative with the following two exceptions, a linear cranial defect in the right frontal bone, 1 inch wide and 5 or 6 inches long, and a kyphosis of the vertebral column at the fourth thoracic vertebra. The cranial defect pulsated and was due to the result of the injury sustained nineteen years previously, as was the vertebral deformity.

Lumbar puncture showed the intradural pressure to be 14 mm. Hg, with clear spinal fluid which did not clot on standing. This specimen contained 2 cells, no globulin and the Wassermann test was negative. A cisterna magna puncture was performed with the intention of introducing lipiodol into the spinal canal to verify the level of compression obtained by the neurologic examination. The intracisternal pressure registered on spinal mercurial manometer was 10 mm. Hg. The fluid was clear. Ten cubic centimeters of fluid was removed and 1 cc. of lipiodol was injected. The lipiodol employed was the same material as used by Sicard and imported from France. Roentgen rays were then taken. The following day another lumbar puncture was performed and a few cubic centimeters of spinal fluid under 14 mm. Hg of pressure were removed. One cubic centimeter of lipiodol was introduced at the lumbar site and the patient turned with his buttocks elevated and his head more dependent so that the oil could gravitate down to the site of the obstruction; Roentgen rays were taken in this position. The Roentgen rays were reported to show the opaque material opposite the seventh, eighth and tenth dorsal vertebræ. This localization did not correspond with the clinical diagnostic level which was the eighth dorsal segment and would be opposite the sixth thoracic vertebra. The difference was so small that it was felt to be confirmatory evidence of spinal obstruction and compression. Operation was advised. The patient left the hospital and was readmitted for operation on May 13, 1924.

On readmission the only change that was noted was in reference to the sensory level. The pain level corresponded to the eighth dorsal vertebra, that is, the eleventh thoracic segment. The preoperative diagnosis was compression fracture of the fourth dorsal vertebra with meningomyelitic adhesions extending from the eighth to the eleventh dorsal segments.

At operation an incision was made extending from the third to the eighth dorsal vertebra, the muscles retracted and the vertebræ exposed. The spinous processes and laminæ of the third, fourth, fifth and sixth thoracic vertebræ were removed and the dura exposed. The fifth and sixth dorsal vertebræ were found fused. The dura was incised, and at the fourth dorsal vertebra, the site of the kyphosis, the spinal cord was somewhat kinked at that point. Both the dura and the arachnoid were very much thickened. No adhesions

were found and the compression was felt to have been caused by the kyphosis of the fourth dorsal vertebra, together with the fusion of the fifth and sixth thoracic vertebræ, and the flexion of the spinal cord at that point. The dura was left unsutured in the closure of the wound. A spinal decompression was really performed. The patient left the hospital on May 27, 1924, two weeks after admission. The postoperative diagnosis was compression fracture of the fourth dorsal vertebra, fusion of the fifth and sixth dorsal vertebræ and an incomplete transverse myelitis of the cord together with some chronic posttraumatic arachnoiditis.

On October 8, 1924, the patient was readmitted to the hospital in a markedly worse condition. His complaint was that his legs "shook," by which he meant that his legs would voluntarily enter into clonus; besides the spasticity had so increased that it was very difficult for him to walk with even the aid of canes. The lower part of the back was beginning to give paresthetic symptoms.

The neurologic examination at this time was as follows: The upper deep reflexes were active and equal; the lower ones, markedly exaggerated and pathologic. The patellar and suprapatellar reflexes were very active. The Achilles reflex entered into permanent clonus on the slightest percussion; the Babinski, Chaddock and Oppenheim reflexes were present on both sides, the Gordon reflex only on the left and the Hoffmann reflex only suspiciously on the left. The superficial abdominal reflexes were all absent, the cremasterics present on both sides. The cranial nerves were negative in the main, with very slight exception, namely, a possible slight paleness of the temporal side of the right disc; the fundal vessels and pathologic cup were normal, and a bilateral nystagmoid movement, more marked on looking to the right, was observed. The sensory examination revealed multiple, patchy areas of disturbances, grading from complete anesthesia into marked hypalgesia and hypesthesia. These findings were more marked on the left side and extended from the eighth or ninth thoracic segment down. Ataxia, adiadochokinesis and tremor of the upper extremities were absent. This patchy distribution of the sensory changes together with an ill-defined level brought the possible diagnosis of multiple sclerosis into serious consideration. A Roentgen ray of the spine showed a portion of the opaque material (lipiodol), which was introduced into the spinal canal on May 7, 1924 (five months previously), lying opposite the seventh, eighth and tenth thoracic vertebræ. The patient was discharged on October 10, 1924, with the diagnosis resting between multiple sclerosis of the spinal form and spinal leptomeningeal adhesions extending from the eighth to the tenth dorsal levels together with the presence of the foreign body lipiodol.

The patient was readmitted for operation on October 22, 1924. He was subjected to another laminectomy on October 24, 1924. The spinous processes and laminæ of the seventh, eighth and ninth

thoracic vertebræ were removed; the dura incised and joined to the incision made at the previous operation. Dense recent leptomeningeal as well as meningomyelitis adhesions were found; the arachnoid was very much thickened and there was no question but that the damage to the tissues noted at this operation had been produced since the last exposure of the canal. Two arachnoidal cysts, one the size of a green pea and the other the size of a kidney bean, lying opposite the eighth and tenth dorsal segments contained lipiodol; these were incised and the oil liberated. It was felt that these encysted masses, aside from producing spinal-cord compression, had recently caused an inflammatory process which resulted in the new lesions noted above. The dura was again left open and the muscles and fascia closed over it. The patient was discharged, December 18, 1924, without any improvement resulting from the operation. He was seen several times later, but improvement had not occurred; in fact, it appeared as if he were growing progressively worse.

Comment. This case demonstrates beyond a doubt that the only possible factor responsible for the increase in the intraspinal condition, which was plainly visible to the naked eye, must be attributed to the irritative action of the lipiodol. At the time of the first operation the dense adhesions between the leptomeninges and the spinal cord and the advanced picture of the arachnoid thickening which were found at the second exposure were absolutely lacking. The pathologic state was altered to a severe extent within a period of five months which was the duration of the lipiodol encystment in the subarachnoid space. It was obviously evident that the progression in the clinical manifestations could be unbiasedly and solely laid to the action of the lipiodol.

The obnoxious result obtained in this one case sufficed for me to abandon the use of this substance in all future instances. I much prefer to rely upon my neurologic findings for localization without the assistance of any such possible drastic measures. It is a horrible experience that one does not wish to witness more than once in his practice, if at all.

Any substance that may remain in the subarachnoid space for years must, if unremoved, produce at least enough tissue reaction to become walled off. This amount of reaction in this situation is sufficiently deleterious to warrant the use of lipiodol to be discarded. Nerve tissue, one must remember, does not regenerate once it is destroyed. All central nervous tissue destruction is permanent and inflammatory processes here produce permanent damage.

To assume that reactions may not occur from the lipiodol, one need only recollect that all foreign bodies lodged in the human body, regardless of the situation, tend to produce a protective fibrous capsule and thereby become encysted. The case reported has given me enough vivid evidence that nerve tissue reacts in

the same general manner as all other tissues, at least in respect to foreign bodies. It is difficult to conceive that a substance composed of such a high percentage of iodin should not have some irritative effect upon such delicate structures as the spinal cord with its coverings.

Aside from Ayer and Mixter,[7] who also advise against the indiscriminate use of lipiodol or iodipin, I am not aware of any other authors who have published cases with harmful results. This reported case is the only one I have knowledge of where the actual tissue changes before and after the use of lipiodol were visually observed and recorded. It may be possible that this particular individual's condition was one where lipiodol was contraindicated in that the original injury was fertile soil and was conducive to the formation of adhesions upon the slightest provocation.

I feel that lipiodol should be employed only as a last resort, and should be entirely restricted to those cases where laminectomy is to be performed within a few days, at which time the oil can be liberated from the canal. No doubt that the several authors who reported the successful use of lipiodol as a localizing agent in spinal-cord neoplasms removed the oil at the time of the operation, and therefore none of the possible irritative effects were obtained.

Conclusions. 1. Lipiodol—a 54 per cent solution of metallic iodin in a vegetable oil—is almost nonabsorbable.

2. One case is reported wherein the intraspinal damage was definitely increased, owing to the use of lipiodol.

3. Lipiodol can be said to be irritating if left within the subarachnoid space over an indefinite period of time.

4. It is advisable not to employ this new material as a means of localization, except as a last resort and only if laminectomy is to follow within a few days. The oil should then be removed from the intradural space.

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ACUTE TYPHOID CHOLECYSTITIS FORTY-ONE YEARS AFTER ORIGINAL INFECTION.

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We recently observed a patient operated upon for acute cholecystitis without calculi. Bacillus typhosus was obtained in pure culture from the gall bladder. There was a definite history of typhoid fever forty-one years before operation with no symptoms suggestive of gall bladder trouble in the interim.

In reading the available literature we were particularly interested in the following general statements: Osler and McCrae[1] say that typhoid bacilli have been found in the gall bladder of patients who never had typhoid fever. Cholesterol gall stones containing typhoid bacilli have been observed to form, apparently within sixty-eight days of the onset of typhoid fever.[2] "Some hundreds" of cases of typhoid fever were traced to a milk supply from a farm looked after by a typhoid carrier who had had typhoid fever forty-seven years before.[3] Garbat[4] made observations on typhoid convalescents, making cultures from the stools and from the bile obtained by duodenal tube. Of 136 cases thus studied, the bile from 15 per cent still showed typhoid bacilli when 3 consecutive cultures from the stools had been negative.

The following definite statements were made as to the intervals after typhoid fever at which the bacilli were actually recovered from the gall bladder or from gall stones. In *Modern Medicine*[5] it is said that the bacilli may persist in the gall bladder after an attack of typhoid fever for an indefinite period, instances of fourteen, seventeen, and eighteen years being cited. Dowd[6] has reported a case of cholelithiasis in which living typhoid bacilli were found in the gall stones thirty-two years after typhoid fever. Clairmont[7] has reported a case of cholecystitis in which typhoid bacilli were recovered from the gall bladder thirty-eight years after an attack of typhoid fever. He does not state definitely whether calculi were present. This is the longest interval, between the time of the original disease and the recovery of the organisms from the gall bladder, of which we can find a record.

Kehr[8] advised cholecystectomy and drainage of the hepatic duct by a *T* tube in patients known to be typhoid carriers at the time of operation. The drainage tube was kept in place until typhoid bacilli were no longer present in the discharge. He reported 10 cases operated upon in this manner with a successful result in 8.

The history of our case is as follows:

On October 10, 1924, G. C., business executive, aged fifty-seven years, entered Lakeside Hospital complaining of abdominal pain. The pain and nausea had commenced two days before while the patient was in New York City, and were thought to be due to some melon that he had eaten. A diagnosis of indigestion was made, and castor oil prescribed. However, the symptoms persisted and were somewhat aggravated by a railroad journey to Cleveland. The pain was greatest in the upper right abdomen, but it radiated to the back and right shoulder.

The past history was negative with the exception of typhoid fever forty-one years ago. This was a typical case with several intestinal hemorrhages. There can be no doubt as to the clinical diagnosis forty-one years ago, for the patient was attended by the father of one of the authors (L. A. P.), who was accustomed to refer to this illness as an extremely severe case of typhoid fever. After this attack the patient had no symptoms suggestive of gall bladder trouble until the onset of the present illness.

Physical examination showed marked tenderness and muscle spasm over the gall bladder region with the gall bladder palpable as a tender mass. There was no jaundice. Otherwise the examination was negative except for a heart of normal size with no murmurs, but a pulse grossly irregular as to rate, rhythm and volume. The temperature was 38.5°. The blood pressure was 136 systolic and 78 diastolic. The leukocyte count was 12,000.

A diagnosis of acute cholecystitis was made and operation advised.

Operation was performed soon after the admission of the patient to the hospital. A 10-cm. incision through the upper portion of the right rectus muscle revealed an acutely inflamed gall bladder. A few adhesions to neighboring organs were broken up. Aspiration of the gall bladder showed a mixture of pus and bile. No stones were found in the gall bladder or in the ducts. Because of the condition of the patient's circulation it was considered safer to drain the gall bladder than to remove it. A drainage tube was sutured into the gall bladder and an additional cigarette drain was inserted. The remainder of the wound was closed with tier sutures.

The postoperative course was uneventful, the patient leaving the hospital on November 12, with a slight amount of bile still discharging from the wound.

The following is a summary of the bacteriologic examinations made during his stay in the hospital:

October 10. (Day of operation.) Culture made from gall bladder showed Bacillus typhosus in pure culture.

October 14. Culture from drained bile showed B. typhosus in pure culture.

October 14. Culture from urine showed no growth.

October 14. Cultures from feces showed B. coli communis, being negative for B. typhosus.

October 17. Culture from blood showed no growth in forty-eight hours.

October 17. Widal test showed no agglutination for B. typhosus or for B. paratyphosus, α or β.

October 23. Culture from drained bile showed B. typhosus in pure culture.

October 23. Culture from bile in drainage bottle showed B. typhosus and B. coli communis.

October 30. Culture from draining sinus showed B. typhosus in pure culture.

November 12. Culture from feces showed no B. typhosus.

The technic followed in demonstrating this organism as B. typhosus was carried out in the pathological laboratory of Lakeside Hospital. The original culture was made in ordinary nutrient bouillon and subcultures on the Conradi-Drigalski plate medium and also in the carbohydrate serum-water media, according to the method outlined by Hiss and Zinsser.[9]

On December 20, the patient was seen at his home. A culture from the sinus, which still discharged slightly at intervals, and also a specimen of stool were sent to the bacteriological laboratory of the City of Cleveland Heights. The laboratory reported B. typhosus in the culture from the sinus but not in the stool.

Conclusions. Our case shows a longer interval between the original attack of typhoid fever and the recovery of B. typhosus by culture directly from the gall bladder than any case which we have been able to find recorded.

The fact that the stools of our patient were persistently negative for B. typhosus, while the organism was present in the discharge from the cholecystostomy sinus, is of especial interest as corroborating the observations of Garbat[4] which have already been quoted.

The ideal operation in patients known to be typhoid carriers is a cholecystectomy combined with drainage of the hepatic duct until no typhoid bacilli are present in the discharge.

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THE EFFECT OF ROENTGENOTHERAPY ON THE HUMAN HEART

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In a recent experimental study[1] on the effect of direct irradiation on the heart, it was found that no constant or characteristic change occurred in rabbits, when a total dosage comparable to that used in the treatment of human cases was employed. In this study a series of rabbits was radiated at varying intervals, and roentgenograms and electrocardiograms were made frequently to detect any change in the size of the heart or in its mechanism. The hearts were also studied at postmortem. The electrocardiographic studies showed only one rabbit to have any irregularity of the heart action. This occurred immediately following treatment and consisted of a few ventricular extrasystoles. At autopsy a number of the hearts showed a few isolated areas of necrosis and fatty infiltration, but these were not thought to indicate any significant myocardial change caused by the Roentgen ray. They were not unlike the picture of heart muscle during the course of various nutritional disturbances, intoxications and infections. Although this study was considered essentially negative, we thought it might be of value to continue the investigation in human cases because of the increased use of deep radiation over the chest. We were further stimulated by the recent paper of Davis,[2] who found evidence of considerable myocardial damage in dogs subjected to intense radiation over the heart.

Those patients who were undergoing roentgenotherapy for various neoplasms of the chest offered a favorable opportunity for observing the effect of irradiation on the heart. The plan for study was to take electrocardiograms of a series of patients receiving such treatment over the chest, when the hearts had been exposed to the Roentgen rays. In addition to noting any variations in the mechanism of the heart arising during treatment, frequent clinical examinations were made so as to elicit changes in signs and symptoms referable to the circulation. This investigation also included a pathological study of material collected from the Peter Bent Brigham Hospital and the Collis P. Huntington Memorial Hospital for the purpose of noting histologic changes in the myocardium. The pathologic data was obtained from two groups of patients, those who had received irradiation over the chest, and those who were treated elsewhere over the body. Those who were treated over parts other than the chest were included because of the large total dosage

received and to determine any change in the heart because of the toxic effect of the Roentgen rays.

In referring to the chart, it will be found that 17 cases were studied, 9 by means of the electrocardiogram and clinical examination, and 8 at postmortem. Two of the cases which came to postmortem were examined by us frequently during treatment for any possible changes in symptoms or physical signs, but were not studied by electrocardiogram. The remaining 6 of the autopsied cases were followed at the Huntington Memorial Hospital and their clinical records were available for study.

The electrocardiographic study was entirely negative except in 2 cases (Nos. 9 and 12). The first patient who received the greatest amount of treatment (8225 ma.) of the series showed a slight flattening of the *T* wave in all three leads. Whether or not this has any significance it is impossible to say, because the patient first came under observation after treatment had been instituted, so there was no control electrocardiographic tracing. She developed dyspnea and pain in the chest during the course of therapy, but it is difficult to feel that her symptoms were not entirely due to an extensive carcinoma of the pleura. There were no signs of circulatory failure in this patient. The other case (No. 12) showed various irregularities in the electrocardiograms, such as nodal beats, premature auricular beats, sinoäuricular block, premature ventricular beats and interpolated beats. Unfortunately, in this case also no electrocardiogram was obtained before treatment, but at that time the physical examination showed a definitely irregular pulse. This patient, as it will be noted in the chart, received a large total dosage of irradiation, but complained of no symptoms referable to the circulation. The other cases, as mentioned above, were entirely negative by electrocardiogram and physical examination, and they gave no suggestion of cardiac symptoms. The pathological studies showed no evidence of myocardial change, except in the older patients, where there was fatty infiltration, splitting of muscle fibers, fibrosis and so forth; but there was neither hypertrophy nor the histologic picture, as would be expected, of injury produced in the heart muscle.

Discussion. This series is necessarily small because of the difficulty of selecting cases which had received sufficient irradiation over the thorax to justify any final deductions as to the damaging effect on the heart. It was furthermore, impossible to study a larger group at postmortem because the number of suitable cases, both at the Peter Bent Brigham Hospital and the Collis P. Huntington Memorial Hospital, was extremely limited. However, the data, both clinical and pathological, are such that certain deductions may be drawn. In the clinical study there was no symptomatic evidence whatsoever to suggest that irradiation of the chest or elsewhere over the body produced a failure of the circulation, through damage to the myocardium. In those instances where dyspnea and cyanosis developed during the course of treatment the symptoms could be

TABLE—CLINICAL ROENTGENOGRAPHIC AND PATHOLOGIC DATA.

Case No.	Record number.	Age.	Diagnosis.	Region treated.	Total dosage ma. mins.	No. of treatments.	Interval between last observation and treatment.	Electrocardiogram.	Pathological examination of heart.
1	....	10	Hodgkin's	Chest	945*	2	29 mos. 2 days	Negative	Living.
2	21099	64	Cancer of lung	Chest	550*	4	10 mos. 5 days	None obtained	Negative.
3	23117	24	Hodgkin's	Chest	870*	6	7 days	Negative	Living.
4	25877	55	Myelogenous leukemia	Chest	600*	2	1 day 6 days	Negative	Living.
5	25702	52	Hodgkin's?	Chest	600*	2	12 days	Negative	Living.
6	22577	61	Multiple myeloma	Chest	720+	3	15 mos. 23 days	None obtained	Negative.
7	24685	38	Cancer of lung	Chest	708+	2	8 days	None obtained	Negative.
8	2584	36	Malignant lymphoma	Chest	3170+	8	1 day	Negative	Living.
9	21163	50	Cancer of breast, metastases	Chest	8225*	8	2 mos. 19 days	(footnote 1)	Living.
10	25866	36	Myelogenous leukemia	Chest	1080*	3	5 days	Negative	Living.
11	23764	48	Cancer of left testicle with metastases	Chest	2400*	4	4 days	Negative	Living.
12	24802	46	Hodgkin's	Chest	1420*	5	(*a*) same day (*b*) 23 days	(footnote 2)	Living.
13	231334	45	Multiple myeloma	Lumbar, spine, sacrum	1731+	4	25 mos. 18 days	None obtained	Negative.
14	22806	36	Cancer of pancreas	Upper abdomen	5194+	8	8 mos. 18 days	None obtained	Negative.
15	24392	56	Chronic lymphatic leukemia	Spleen, post, chest	1963+	5	9 days	None obtained	Negative.
16	22992	66	Cancer of uterus	Pelvis, anterior, posterior	1377+	4	9 days	None obtained	Negative.
17	17553	45	Sarcoma mediastinum	Neck	1782+	4	6 days	None obtained	Negative.

* Treated at Peter Bent Brigham Hospital as follows: Target skin dist. = 30 cm. K. V. peak = 140. Filter ½ mm. cu., + 1 thickness sole eather.

\+ Treated at Collis P. Huntington Memorial Hospital as follows: Target skin dist. = 80 cm. K. V. peak constant 170. Filter ½ mm. cu.

[1] The electrocardiogram showed a slight flattening of the *T* wave in all three leads.

[2] The electrocardiogram showed premature auricular and ventricular beats, sinoauricular block, etc.

There were no changes in symptoms and signs referable to circulation.

explained by the mechanical interference of the tumor on the intrathoracic structures.

The electrocardiographic tracings were entirely negative, except in the 2 cases already cited; 1 which showed an irregularity of the auricular-ventricular complexes and the second a slight variation from the normal in the *T* wave. Neither patient, however, had symptoms referable to the circulation and the one who showed the electrocardiographic irregularity was known to have had an irregular pulse before the beginning of treatment. In the pathologic studies there were evidences of myocardial changes, but they were not unlike those commonly found in hearts of patients advanced in years or in those who had suffered from infections or debilitating diseases. Although the above results are essentially negative, they do not necessarily exclude the occurrence of temporary changes in the myocardium or the possibility of severe or permanent damage following more intensive irradiation. However, if temporary or mild changes were produced, they were unrecognized by methods of clinical examination. It seems therefore, that until more intensive treatments can be given without damage to the skin, there should be no reason to feel that serious injury to the myocardium may be produced through irradiation over the chest.*

Summary. A series of cases irradiated over the chest were studied by means of electrocardiograms and by clinical and pathologic examination for the purpose of determining any changes in the myocardium which could be attributed to the effects of roentgenotherapy. A series of other cases receiving irradiation over parts other than the chest were also studied. There was no definite evidence to suggest that roentgenotherapy in the dosage used was sufficient to cause any temporary or permanent changes in the myocardium which could be recognized by the methods used in this study. When increased dosage can be used without danger of causing skin or systemic reactions the possibility of injuring the heart will need to be reconsidered.

The kind coöperation of Dr. C. L. Brown during the studies at the Peter Bent Brigham Hospital and the assistance of Dr. Raphael Isaacs in obtaining the data from the Collis P. Huntington Memorial Hospital are acknowledged with appreciation.

* Since this paper was sent to the publisher our attention has been called to an abstract in the Am. Jour. Roent. and Rad. Ther., 1925, **14**, 289, wherein Schweizer described myocardial degeneration following intensive irradiation of a mediastinal tumor. The amount of treatment was not reported in the abstract, and as yet we have not been able to read the original article (Strahlentherapie, 1924, **18**, 812).

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A QUANTITATIVE DETERMINATION OF INTESTINAL PUTREFACTION.

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For the past ten years we have been investigating[1] in our laboratory the chemical defence mechanism of the animal as well as of the human body against various foreign organic compounds, particularly against those compounds which might be considered as resulting from abnormal catabolic processes in the body and against various forms of intoxication resulting from the absorption of poisonous substances in cases of socalled autointoxication, intestinal putrefaction, and the like.

In general, there is an initial attempt on the part of the animal organism to oxidize completely or burn up the foreign molecule; if this is unsuccessful there is an attempt at reduction; finally, if both of these methods fail, an attempt is made to conjugate or join the toxic substance to some compound or radicle which seems to reduce the toxicity and at the same time increase the solubility, making possible the rapid elimination of the resulting compound in the urine. Our findings thus far allow us to state definitely that a given species of animal may have a certain definite mechanism of chemical defence against a given substance, while another species of animal may protect itself in an entirely different way. For instance, mammals, including man, protect themselves against ingested benzoic acid by joining or conjugating it with the amino acid glycocoll; but for the detoxication of the next acid in the series, namely, phenylactic acid,[2] man is the only mammal whose organism conjugates it with the amino acid glutamin. All the lower animals, including the monkey, use glycocoll for this purpose.

We have synthesized in the laboratory many of the products resulting from the putrefaction of protein material in the intestine. With this comparatively large quantity of material to work with, we have been able to study not only the detoxication of the poisonous compounds, but also their physiologic effect upon the body. In general, it may be said that their toxicity is very much less than has been commonly thought, while many of these compounds are absolutely harmless. Most putrefactive products absorbed from the intestine possess both an aromatic nucleus and a side chain, and are not detoxicated by oxidation or reduction but by conjugation. The substances most commonly used for this pur-

pose are four of the amino acids, namely, glycocoll, glutamin, ornithin and cystein; also glycuronic acid, acetic acid and sulphuric acid. Others less often employed are the methyl group and the thiocyanate radicle.

One important feature of the detoxication mechanism is that, although these substances used in chemical defence cannot be stored in the body for emergency purposes, they can none the less be synthesized in many cases from refuse material which would ordinarily be excreted in the urine. Sulphuric acid used in this connection is for the most part derived from the catabolism of the animal's own tissues or from endogenous cystein and would otherwise have been excreted as inorganic sulphates in the urine.[3] The supply is, therefore, necessarily limited, and cannot be replaced by the feeding of sulphates. A failure of the limited sulphate supply calls forth an apparently unlimited supply of glycuronic acid which seems to be derived from the carbohydrate supply of the body but which, as far as our researches have indicated, may also be derived from the sugar-forming amino acids of protein.[4] Glycocoll and glutamin, two of the amino acids occurring in the protein molecule, may be synthesized by the human body simultaneously for the detoxication of benzoic acid and phenylacetic acid respectively,[5] even when the subject is maintained on a nonprotein diet or is fasting. The nitrogen necessary for the synthesis of these amino acids is not derived from the breakdown of body tissue, but is taken from the refuse fraction which would have been otherwise excreted in the urine. Benzoic acid is detoxicated by the bird by joining it with ornithin, another amino acid,[6] which the bird can synthesize for this purpose,[7] taking the nitrogen from that fraction which would have otherwise formed uric acid, the substance corresponding to urea in mammals. Cystein, the sulphur-containing amino acid, cannot be synthesized by the animal body, but is available for detoxication purposes only when protein containing cystein is ingested.[8, 9] The validity of these results have been verified by their subsequent *rediscovery* by various investigators,[10, 11] and authors.[12] The fact that certain amino acids, such as glycocoll, glutamin and ornithin, can be synthesized *in vivo*, while others, such as cystein, cannot be built on demand by the body, gives us the much-needed explanation why we have our two nutritional groups of alpha amino acids—the "essential" and the "nonessential."

In more than 13,000 pages of the literature dealing directly with what may be called the chemical side of intestinal putrefaction, the majority of investigators have attempted to determine the extent of bacterial protein decomposition in the intestine by quantitative determinations of urinary indican, or of skatoxyl; others have used the quantitative determination of ethereal sulphates or of glycuronic acid; a few authors maintain that none of these estimations alone gives one an idea of the extent of abnormal amino-acid dis-

integration. They would rely on the ratio of indican to ethereal sulphate as a rough quantitative index of intestinal putrefaction.

While working in this general field we determined to see how nearly quantitatively we could determine these end products of putrefaction after a given quantity of them had been introduced into the gastrointestinal tract of human beings as well as of certain experimental animals. The latter were for the most part rabbits. The human subjects of these experiments were all over twenty-five years of age, and were maintained on a uniform diet; the bowels were regulated as well as possible. The socalled putrefactive products chosen for the experiments were indol and skatol, both of which are derived from the amino acid tryptophan; phenol, derived from either tyrosin or phenylalanin; imidazol, as well as imidazol acetic acid, derived from histidin. The indol and skatol for the human subjects were ingested in small gelatin capsules coated with salicin to insure that the capsule would open in the intestine rather than in the stomach. Each capsule contained 0.05 gm. of the substance. The phenol was simply drunk in a 0.1 per cent solution; imidazol and imidazol acetic acid as dilute aqueous solutions of their soluble hydrochlorids. The rabbits received the water-soluble substances by means of a stomach tube; the skatol and indol, being nearly insoluble in water, were poured down the tube in the form of an emulsion, formed by soaking the substances for some time in warm water and then shaking vigorously. The human urine was collected in twenty-four-hour periods and that of the rabbit in forty-eight-hour periods. On each collection duplicate determinations were made for total nitrogen, urea, ammonia, uric acid, and inorganic, ethereal and reduced sulphur. In addition to these, glycuronic acid was determined in all the urines. On the indol urines determinations were made for free indol and indican (indoxyl potassium sulphate), according to the method of Jolles[13] as well as the older and better known method of Obermayer.[14] Urines collected after the skatol feedings were examined for skatoxyl potassium sulphate and for skatol, in addition to the regular routine analysis, while the phenol urines were examined especially for phenol. The urines collected after feeding imidazol and imidazol acetic acid were examined quantitatively for imidazol derivatives, according to the test of Koessler and Hanke.[15] As the dosage was relatively small, the feces were neglected. Skatol is perhaps, if anything, more toxic than the indol. Both of these substances caused no distress after 0.05-gm. doses, but after 0.1 gm. there was a distinct feeling of nausea, but no vomiting, followed by loss of appetite, belching and a dull headache which persisted for at least twelve hours after a dose of this size. Phenol had no untoward effects. The imidazol compounds caused a slight but noticeable increase in the pulse rate of 10 to 20 per minute. Two kilogram rabbits were able to receive as much as 0.05 gm. of indol

or skatol without losing their appetite and double this dose of phenol; but as much as 0.1 gm. of indol or skatol caused the animal to remain stupidly in the corner of his cage, showing no inclination toward food but a great desire for water. As much as 0.1 gm. of either imazol or imidazol acetic acid can be fed to a rabbit every three hours without causing more than slight muscular spasms.

TABLE I.—INDOL.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted as indican (Obermayer's test).	Per cent excreted as indican (Jolles's test).	Total per cent.
Human	50	...	11	...	35	65	11 35 65
	50	...	39	...	31	56	39 31 56
	100	3	52	12	79	121	67 79 121
	50	...	10	...	44	66	10 44 66
	80	30	28	...	28	102	58 28 102
Rabbit No. 1	100	45	13	...	77	96	58 77 96
	150	69	35	...	88	180	104 88 180
	200*						
	70	...	33	6	41	75	39 41 75
Rabbit No. 2	100	26	...	...	74	132	26 74 132
	150	78	21	...	122	240	78 122 240

* Rabbit died after one hour.

It may be seen from Table I that indol is but slightly detoxicated by combination with sulphuric acid and far less by a combination with glycuronic acid. A considerable amount is excreted free or uncombined whenever the amount ingested exceeds about 50 mg. Since the indoxyl sulphuric acid and the indoxyl glycuronic acid taken together never correspond to the values for indican as obtained by the Obermayer test or the Jolles test, we may conclude either

that the tests for sulphates and glycuronic acid are faulty, or else that indol itself contributes to the indigo formed on oxidation, perhaps through some intermediary reaction as yet not understood. Another point is that the sum of the unchanged indol and the indoxyl potassium sulphate (or indican) and the indol glycuronic acid never equals 100 per cent. Again the figures for indican as obtained by either the Obermayer or the Jolles test are neither consistent nor comparable. We are inclined to believe that the latter test is nevertheless more satisfactory than the older Obermayer test, which invariably carries the oxidation too far, causing a considerable formation of isatin at the expense of the indigo. Besides, in addition to the indigo blue, there is a good deal of indigo red formed; if this is taken into consideration it must be treated first with 10 to 20 per cent sodium hydroxid solution, causing a molecular rearrangement to indigo blue. While Obermayer's test gives consistently low results for indican, Jolles's test gives on the whole results much too high. Our work indicates that glycuronic acid serves only in a minor capacity as detoxicating agent for indol, and is apparently used only after the sulphate supply has been nearly exhausted. The excretion of the glycuronic acid compound, if detected at all, begins usually twelve to eighteen hours after the ingestion of the indol.

TABLE II.—SKATOL.

Subject.	Amount fed in mg.	Per cent. excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted unchanged.	Total per cent.
Human	50	114	..	12	126
	50	82	..	18	100
	150	90	..	32	122
Rabbit	70	66	..	48	114
	100	15	22	33	70
	150	20	..	41	61

It may be seen from Table II that skatol is for the most part detoxicated by conjugation with sulphuric acid and excreted as the ethereal sulphate rather than as a glycuronic acid compound. It is to some extent excreted uncombined, but contrary to the accepted theory, skatol seems to be more easily oxidized to skatoxyl than indol to indoxyl.

TABLE III.—PHENOL.

Subject.	Amount fed in mg.	Per cent excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted unchanged.	Total per cent.
Human	50	18	..	..	18
	100	24	22	12	58
	150	22	36	28	86
Rabbit No. 1	50	48	..	25	73
	100	33	..	61	94
	150	22	12	79	113
Rabbit No. 2	100	36	..	28	64
	150	40	19(?)	56	115
	200	21	..	84	105

Phenol is detoxicated chiefly by joining it with sulphuric acid. The supply of this seems to be derived not only from endogenous catabolism, but also from cystein of exogenous origin, and hence the percentage of phenol detoxicated in this way is dependent on the sulphur-containing protein in the diet. This makes ethereal sulphate determinations a very uncertain indicator of the amount of phenol present.

TABLE IV.—IMIDAZOL.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as urea.	Per cent excreted as uric acid.	Per cent excreted as ammonia.	Total per cent.
Human	50	23	..	..	..	23
	100	31	..	3	..	34
	150	33	..	8	..	41
	200	56	..	19	12(?)	87
Rabbit	100	42	..	..	..	42
	150	59	..	12	..	71
	250	66	..	8	..	74
	500	74	..	12	..	86

TABLE V.—IMIDAZOL ACETIC ACID.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as as urea.	Per cent excreted as uric acid.	Per cent excreted as ammonia.	Total per cent.
Human	50	42	..	..	..	42
	100	68	..	..	..	68
	200	79	..	13	6	99
Rabbit	100	36	..	..	..	36
	200	60	..	6	..	66
	500	81	..	22	..	103

Imidazol and imidazol acetic acid in Tables IV and V were merely estimated colorimetrically. Other work in our laboratory concerning these substances has shown us that the imidazol ring is not oxidized with the formation of a hydroxy compound capable of joining with sulphuric acid and glycuronic acid. On the other hand, it seems to split into uric acid to some extent, and perhaps also into urea and ammonia. Both in the case of the human and the rabbit uric acid seems to be quite a constant derivative from the imidazol ring alone and to a lesser extent from the acetic acid derivative, but the indications are too uncertain to be of value. The test for imidazol itself is quite sensitive but rather elaborate; it is very doubtful whether these histidin derivatives are of sufficient physiologic or pathologic importance to receive so much attention.

It is quite evident that none of our socalled quantitative tests for the best-known putrefactive products in the urine are much more than a rough estimate of the amount of indigo formed in a given quantity of urine by the action of some oxidizing agent like ferric chlorid, and this estimate only a colorimetric one.

At the present time we are attempting to standardize a clinical method for the determination of indol, indoxyl and phenols in the blood, thus giving a first-hand knowledge of any abnormal processes

taking place in the intestine. In addition to this we are taking a number of the ethyl amine derivatives of the alpha amino acids of protein, derived by a splitting of CO_2 from the carboxyl groups of these acids, and we are feeding them to humans as well as to animals to determine their toxicity as well as the course they take in the process of detoxication.

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(LEFT) SHOULDER PAIN OF PHRENIC ORIGIN—A REFLEX SYMPTOM IN CHRONIC APPENDICITIS.

With a Report of Three Cases.

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Phrenic shoulder pain associated with irritative conditions of the diaphragm is readily recognized, but the association between pain in the left shoulder and a diseased appendix is seldom thought of. Reflex symptoms in chronic appendicitis, according to Rolleston,[1] belong to those complaints which are characterized by hypertonus and spasm of the stomach, as well as by failure on the part of the pyloric and ileocecal sphincters to relax.

Spasm of the pylorus associated with chronic appendicitis leads to increased gastric pressure. The accommodating factor for this increased gastric pressure is the gas bubble of the stomach. The mechanism by which the pain is referred to the left shoulder region is brought about by a pylorospasm, increased intragastric pressure, upward pressure upon the left diaphragm by the fornix (fundus) and irritation of the phrenic nerve. The phrenic nerve arises chiefly from the fourth cervical nerve with a filament from the third and a communicating branch from the fifth. Its termination

is in the diaphragm, where some branches are distributed to the thoracic surface and some which pierce the diaphragm are distributed to its under surface. In its origin the phrenic nerve is in communication with the descending branches of the cervical plexus. These branches become cutaneous near the clavicle. Thus we see how pain in the left shoulder region may occur when the left phrenic nerve is irritated as a result of reflex pylorus spasm in chronic appendicitis.

The association between a diseased appendix and pain in the left chest, neck or shoulder region was first called to my attention about four years ago by Dr. Emanuel Libman, during ward rounds at Mt. Sinai Hospital.

Bassler[2] reports a case of chronic appendicitis simulating angina pectoris in a man aged fifty years, whose symptoms were entirely relieved by appendectomy.

Sir Humphrey Rolleston[3] divides the symptoms of chronic appendicitis into four groups—reflex, mechanical, toxic and infective.

In the 3 cases that have come under the writer's observation the symptoms were of reflex origin and were not due to an infection of the phrenic nerve.

Case Reports. CASE I.—W. R. B., a man, aged twenty-eight years, had given a history of having had two previous attacks of appendicitis, at twenty-four and twenty-eight years of age. Each attack was associated with pain and tenderness in the right lower quadrant, vomiting and fever. With rest in bed and local applications of ice the acute symptoms subsided, but the patient continued to complain of heartburn, acid regurgitations and pain in the left shoulder region shortly after meals. This pain would gradually subside between meals to recur again soon after the next meal. He first came under observation, November 3, 1924, complaining of these symptoms and with the history as above stated.

Family History. One brother was operated on for acute appendicitis in 1920. The patient's past history was irrelevant, except for gastrointestinal disturbances such as heartburn, regurgitation of acid secretion and occasional attacks of pain in the right lower quadrant during the past three years associated with constipation.

During the past three months gastric symptoms had become more aggravated. There was a dull pain in the left shoulder region which lasted for about two hours after meals and then gradually subsided. There was also a feeling of distention in the lower abdomen. The appendectomy was advised and performed, and since then the patient has had no further attacks of left shoulder pain and has been free of all symptoms.

CASE II.—J. A. L., a young girl, aged nineteen years, who had her first attack of acute appendicitis in 1921, has been complaining

since then of a feeling of distress in the epigastrium soon after meals with pain in the left chest and shoulder region which was generally relieved by belching. These symptoms persisted for about two years, when a second attack of acute appendicitis brought her to the hospital for an operation. Since then the patient has been free of all symptoms.

CASE III.—H. B., a male, aged twenty-three years, who had been complaining of pain in the left shoulder region with epigastric fullness and heart burn during the past four years. One or the other of his symptoms would usually predominate constantly. There was no history of any acute appendicitis that the patient could remember, although he gave a history of having attacks of stomachache as a child.

There was tenderness in the right lower abdomen on all examinations and a Roentgen-ray examination of the gastrointestinal tract showed evidences of a pylorus spasm and an appendix which was fixed, tortuous and filled for a period of one hundred and twenty hours. The appendix was removed three months ago and since then the patient has been free of symptoms.

Held,[4] in a recent comprehensive article on chronic appendicitis, has properly divided the reflex symptoms into those associated with motor, sensory and secretory phenomena.

1. *Motor Phenomena.* These are evidenced by increased spasm and tonus of the sphincters of the alimentary tract. Moynihan[5] observed marked gastric contractions and spasm of the pylorus or other parts of the stomach while he was removing a chronically diseased appendix. His term, "appendicular dyspepsia," very correctly designates that syndrome of gastric symptoms associated with appendicular disease. Hurst[6] observed spasm of the greater curvature during a fluoroscopic examination when he exercised pressure over the area of the diseased appendix. The delay he enountered in the ileum he believed to be due to a spasm of the ileocecal sphincter. Disturbances in motility of the colon with spasm in its various parts is also present and explains the spastic constipation and the pain over the sigmoid area that sometimes occurs. Held calls attention to the fact that chronic appendicitis may at times cause loss of tone in the various parts of the gastrointestinal tract.

In these cases associated gastric atony or the atonic type of constipation may be responsible for a great many of the symptoms encountered. The writer also states that there may occur symptoms of hypertonus and spasm in some parts of the gastrointestinal tract and loss of tone in other parts. It has been the experience of Held that in chronic appendicitis there is often atony of the stomach and spasticity of the cecum or the descending colon.

2. *Sensory Phenomena.* The reflex sensory disturbances manifest themselves by the presence of pain in the epigastric region. Mackenzie[7] believes that the pain is referred through the sixth and seventh dorsal nerves which terminate in the abdominal walls. Hurst states that the pain is visceral due to hyperperistalsis in the pyloric end of the stomach. Both agree that an irritated focus in the spinal cord is responsible for the increased sensory disturbance obtained by pressure over the skin and muscles in the epigastric area.

If the irritated focus in the spinal cord is in the region of the fourth or fifth dorsal nerves the pain may be thoracic and simulate attacks of stenocardia. If the irritating center is low in the spinal cord pain may radiate down the right thigh or to the urinary bladder. It is well known that when the appendix is situated behind the cecum there may be direct pressure on the ureter with attacks that simulate renal colic. The irritation may even cause red blood cells to appear in the urine. In these cases the symptoms are not reflex but due to direct pressure.

3. *Reflex Secretory Phenomena.* These are evidenced by disturbances in gastric secretion and also by disturbances in the colon. Gastric hypersecretion and hyperacidity are frequently met with, whereas lowered acidity is rare. Attacks of cramps in an associated mucous colitis with discharge of large quantities of mucus occasionally alternating with an attack of serious diarrhea has been reported. Held mentions the fact that frequent urination may be one of the reflex secretory phenomena, but believes that the gastric hyperacidity is responsible for an alkaline urine, thus causing irritation in the urinary bladder and frequency in micturition.

That reflex symptoms vary in different individuals in chronic appendicitis or even in the same individual is often the case. With a depression in the motor function there come a group of symptoms which are entirely different from those associated with a hypertonus of the various sphincters of the gastrointestinal tract. Where the secretory phenomena predominate heartburn, regurgitation of acid secretion or vomiting may occur. It is in this type that the differential diagnosis from gastric or duodenal ulcer is extremely difficult. In a certain number of cases it is known that a chronic appendix may coëxist with a duodenal ulcer.

Cope[8] points out that any condition which may cause irritation of the diaphragm or the contiguous tissues supplied by the phrenic nerve may be the cause of phrenic shoulder pain. It is clear, therefore, that diseases of the liver, stomach, duodenum, pancreas, and so forth, will most commonly cause the pain. He had known the pain to be of diagnostic value in a number of conditions, appendicitis being among them.

He states, however, that it is seldom that phrenic shoulder pain is a symptom in appendicitis, for the very good reason that it is

uncommon for the infection to extend up to the diaphragm. With a long ascending appendix, however, or in the cases where the cecum and the appendix are much higher than normal the symptom is to be expected. The author can only find references to 2 or 3 such cases in the Continental literature, and he himself has known of only 2 cases in which such shoulder pain occurred. He reports a case as follows:

R. M. was taken with acute abdominal pain, followed about fifteen hours later by severe pain over the right acromial region. A perforated retrocecal abscess was found at operation, and there was a great amount of seropurulent fluid in the abdominal cavity. For three weeks after operation slight pain continued to be felt in the right shoulder on deep inspiration. The initial pain in this case was described as that of a nail being driven into the acromioclavicular joint. It is specially to be noted that the pain in this case was not felt on top of the shoulder until some hours after the abdominal pain. This was also exemplified in the second case, in which pain was felt over the right clavicle twelve hours after the onset of the abdominal pain. At operation an inflamed ascending appendix with spreading peritonitis was found, and some lymph was noted in front of the liver.

Orr[9] states that the shoulder and neck pain, frequently produced in disease involving the diaphragm, is not given its proper importance as a diagnostic aid. The following is a list of conditions in which phrenic shoulder pain or neck pain has been described: Pneumonia, pleurisy, pericarditis, pulmonary infarct, actinomycosis of lower right lung, liver abscess, cholecystitis with peritonitis, perforation of the gallbladder, perisplenitis, appendicitis, ruptured extrauterine pregnancy, pressure of drainage tube and suprarenal tumor. Referred pain to the shoulder or neck is characterized by its spontaneous appearance, and its accurate localization in the distribution of a spinal segment or to a small portion of the segmental sensory distribution, by accompanying hyperesthesia and hyperalgesia and often by increase of pain during deep respiration, cough or change of position. At times the pain is quite severe. In many diseases, especially those in the abdomen, the existence of a shoulder or neck pain is a distinct aid to diagnosis. Its presence is definite evidence that the sensory distribution of the phrenic nerve is involved in the irritation. To be of value, referred shoulder and neck pains must be carefully differentiated from pain due to disease in and about the shoulder. In those diseases having a direct contact with the diaphragm it is quite clear that the pain is referred through the third, fourth or fifth cervical nerves. Shoulder pain in acute appendicitis is rare. To produce such pain it is, of course, necessary for infection to come in contact with the phrenic

nerve. The length and location of the appendix may be factors in this involvement. It is well known how frequently subdiaphragmatic inflammation follows suppurative appendicitis. Evidence of phrenic nerve irritation in such a condition may be of great value. The writer concludes that the diagnostic value of phrenic shoulder pain is definite. When typical it is a positive indication of an irritation to the phrenic nerve and should be sought where disease is suspected in the upper abdomen or lower chest.

In the opinion of the writer of this paper, one should add diseases of the lower abdomen, especially chronic appendicitis, to those that cause phrenic pain in the region of the left shoulder. In the 3 cases reported, there was an associated pylorospasm with increased gastric tension and upward pressure on the left diaphragm which proved to be the cause of the phrenic shoulder pain.

Summary. Three cases are reported in which pain in the left shoulder was associated with chronic appendicitis, acting reflexly through the phrenic nerve, disappearing following appendectomy. The method of production of the pain is discussed.

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REVIEWS.

DISEASES OF THE BRONCHI, LUNGS AND PLEURA. By FREDERICK T. LORD, M.D., Visiting Physician, Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Second edition, thoroughly revised, with the addition of a chapter on Pulmonary Tuberculosis. Pp. 776; 110 illustrations. Philadelphia and New York: Lea & Febiger, 1925. Price, $8.00.

THE physician and the student will find in this work a complete accurate conservative statement of the subject. The thoroughly revised second edition takes full cognizance of recent advances in this field, and of these there have been many. Bronchoscopy has become an invaluable aid to the clinician in the diagnosis and treatment of chronic lung suppuration, foreign body and the various types of tracheal and bronchial stenosis. There have been improvements in Roentgen-ray technic and in thoracic surgery. These are fully appreciated and well presented, as is the newer knowledge of bronchial asthma, of the immunity phenomena of tuberculosis and of the factors underlying recovery and resolution in lobar pneumonia. There has been added in this edition an excellent chapter dealing with pulmonary tuberculosis. A few minor criticisms apply: In regard to the treatment of bronchial asthma, the statement that "The subcutaneous injection of plant pollen, horse-hair protein, or other substances to which the patient is sensitive, is dangerous, and there are no convincing reports in the literature of success by this means," is not wholly in accordance with the facts, especially in the case of pollen asthma. Hereditary telangiectasis is not given among the possible causes of hemoptysis.

R. K.

THE SURGERY OF PULMONARY TUBERCULOSIS. By JOHN ALEXANDER, B.S., M.A., M.D. Pp. 356; 53 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $4.50.

VERY recently surgery has come to the fore in the treatment of pulmonary tuberculosis of the advanced type, especially in those

cases where other types of treatment have failed to benefit. Surgery today is curing or improving approximately two-thirds of such cases. This work, the first in the English language, presents the entire subject, both for the practitioner and for the surgeon. The detail of diagnosis, and the description of the character of the cases in which surgery should be done, is especially for the edification of the general practitioner. The surgical treatment of pulmonary tuberculosis is one that has been forced upon the American surgeon, as the Continental surgeons have gone further and further away from us in their advances in this direction. The author gives to the reader an up-to-date conception and understanding of the status of affairs today. It is stated in the work that 60 per cent of the patients upon whom radical surgery has been attempted for the amelioration of pulmonary tuberculosis are markedly improved. The work is extremely interesting, as it is new to most of us readers.

E. E.

DISEASES OF THE NOSE, THROAT AND EAR. By WILLIAM LINCOLN BALLENGER, M.D., late Professor of Otology, Rhinology and Laryngology, College of Physicians and Surgeons, University of Illinois. Revised by HOWARD C. BALLENGER, M.D. Fifth edition. Pp. 1080; 569 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $10.00.

THE fifth edition of the author's *Diseases of the Nose, Throat and Ear* begins with a complete description of the anatomy and physiology of the nose. The obsolete operations of the nasal septum, such as the Gleason, Bosworth, etc., are still described in detail. The submucous resection is beautifully illustrated and easily understood. Most modern methods of treatment, medically and surgically, of the accessory sinuses are given with beautiful illustrations.

The tonsil question is taken up in detail. Indications for local and general anesthesia. Various operations are described, particularly the Sluder, Ballenger's modification and the dissecting method. The larynx is fully considered, from simple laryngitis to total laryngectomy.

The chapter on the ear is systematically and clearly written with beautiful illustrations of the simple and radical mastoid operations and its complications. The physiology and pathology, and the newer operations of the internal ear, are well described and illustrated. At the end is a bibliography and an index. This work is one of the best published to date and is well worth possessing and reading by students, general practitioners and specialists.

D. H.

PREVENTIVE MEDICINE. By MARK F. BOYD, M.D., C.C.H., Member of the Regular Field Staff, International Health Board of the Rockefeller Foundation. Second edition. Pp. 429; 135 illustrations. Philadelphia and London: W. B. Saunders Company, 1925.

THE practitioner or medical student will find in this enlarged edition, a work which amply fills his requirements in the field of preventive medicine, while the teacher of hygiene will appreciate its value as a reference book. The topics range from epidemiology to the hygiene of infancy and from demography to ventilation and exercise. Except for a few chapters which are arranged in rather too tabular a form, the book makes "interesting reading," and certainly contains a vast amount of useful information.

J. A.

PERSONAL AND COMMUNITY HEALTH. By CLAIR ELSMERE TURNER. Pp. 426; 53 illustrations. St. Louis: C. V. Mosby Company, 1925.

THE book presents the facts of healthful living and the scientific principles upon which health practices rest. The public health is considered from the standpoint of what the college and professional man, who is not a sanitarian, needs to know to protect his family and meet his responsibility as a citizen.

Chapters are devoted to various phases of personal hygiene. The science of disease prevention is presented in several chapters. Other chapters deal with food control, water supply and waste disposal. In appendices are given brief explanations of the essential facts in the control of communicable diseases and in the use of disinfectants.

The subject is treated in a logical manner and in convincing style. The book should appeal to that large group of persons who are no longer in college.

D. B.

AN INDEX OF TREATMENT. By VARIOUS WRITERS. Edited by ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital and Physicians to the Hospital for Sick Children, Great Ormond Street; and JAMES SHERREN, C.B.E., F.R.C.S., Surgeon to the London Hospital and Consulting Surgeon to the Poplar Hospital for Accidents. Ninth edition, revised and enlarged. Pp. 1035; 108 illustrations. New York: William Wood & Co., 1925.

THIS textbook, now well known in this country, is of real value to the general practitioner for whom it was written. The intro-

ductory chapter on the general principles of treatment by the senior editor is full of common sense and inspires confidence in the great mass of detailed data that follows. Of the ninety-six British contributors some are internationally known and all have good hospital connections. The subjects are alphabetically arranged, quite concisely handled and include most of the medical and surgical conditions commonly encountered in practice. It is surprising, however, to find no mention of pneumoconiosis or spirochetosis icterohemorrhagica and only a single and very inadequate paragraph on the subject of purpura. Furthermore, a tendency to give undue attention to the use of drugs in certain conditions is noted, and a neglect of other more rational procedures. No mention, for instance, is made of transfusion in the treatment of shock, although pituitrin and adrenalin are recommended. On the whole, nevertheless, the book meets a need and the reviewer is glad to have it on his shelf. T. M.

ARTERIOSCLEROSIS: A SUMMARY VIEW. By the late RT. HON. SIR T. CLIFFORD ALLBUTT, P.C., K.C.B., M.A., M.D., F.R.S., etc. Pp. 108; no illustrations. London: Macmillan & Co., 1925.

AN essay in six chapters, enlarged from a postgraduate lecture at Cambridge, this booklet summarizes the author's views on this complex subject. Seen through the press after the death of its distinguished author last February by his successor, Sir Humphrey Rolleston, who contributes a short note, the book substantially repeats the views expressed in the larger work, *Diseases of the Arteries*, which was published in 1915. The first chapter on "Meanings" is especially valuable in defining the field and as an illustration to medical writers of the value of precision in terms and expression.

Many may not be willing to accept the author's view that *hyperpiesia* (to be distinguished from the hyperpiesis of chronic Bright's disease) is a distinct disease, probably due to some "warp in metabolism," which turns out some pressor amine or fails to excrete it. They will find, nevertheless, edification in the impartial presentation of the earlier chapters and practical advice of value in the chapter on Therapeutics. Only one typographical error was observed—"stony" for "atony," on page 41.

A hasty survey of the authorities quoted shows about 100 out of 150 by English authors and only 20 in foreign languages! Such a disproportion, to say the least, emphasizes the handicap placed on scientific internationalism by the curse of tongues. E. K.

THE MEDICAL FOLLIES. By MORRIS FISHBEIN, M.D., Editor of the *Journal of the American Medical Association*. Pp. 223. New York: Boni & Liveright, 1925.

A CONTINUATION of the American Medical Association's energetically conducted campaign of propaganda against quackeries of all sorts, this book contains most of the strong and weak points of this popular form of human endeavor. Undoubtedly, it is "a book with a wallop," and should appeal to the intelligent and impartial layman when the two are placed in contact. While its influence is thus clearly for good, one cannot but feel that an even stronger impression would be made if a less intolerant attitude were adopted toward those "follies" that are not arrant quackery and knavery, and less emphasis were placed on the powerful organization that the author represents. The inroads of osteopathy and chiropractic may be estimated from the fact that one-quarter of the space is given to these two of the fourteen chapters. In the description of the earlier cults, a calmer historical spirit prevails—as one would expect from the secretary and editor of the Society of Medical History of Chicago—and the final chapter is a strong plea for a rational attitude toward the science of healing. In picturesque description the high point is reached in the excerpts from Andrew Still's autobiographic notes, which take us back to Fifteenth Century Italy in their Cellini-esque style. E. K.

METHODS IN SURGERY. By GLOVER H. COPHER, M.D. Pp. 232. St. Louis: C. V. Mosby Company, 1925.

THE author takes up in detail the routine procedures that have to be performed in the daily life of the average hospital. The book is prepared after the technic and regime used at the Washington University School of Medicine, in the Barnes Hospital and the St. Louis Children's Hospital. He devotes the first chapter to information with regard to history-taking and physical examination in detail. Subsequent chapters take into consideration the running of the various departments of the hospital and the professional interrelationship between the residents, the nurses, the staff and the department officers of the hospital. The pre- and post-operative care and many of the minute surgical procedures are outlined in detail. The book is an excellent one from the standpoint of telling one how to get along in a hospital, and could well be recommended to all students about to undertake a resident or internship at any hospital. Perusal of this little book will prevent many unfortunate, irritating and a few serious mistakes.

E. E.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Uremia and Nephritis.—In this address before the Toronto Academy of Medicine, MEAKINS (*Canadian Med. Assn. J.*, 1925, **15**, 771) discusses the functions of the kidney and then very briefly discusses what is uremia. He says very truthfully that we do not know just what is the cause of this condition, which primarily is due to some cellular disturbance. The blood reflects in part this disturbance, but it is certainly doubtful if it does so accurately under abnormal conditions when the blood may be altered by a disturbance of the water balance, a disturbance of the acid-base equilibrium and an alteration of the relative importance of the inorganic constituents of the body fluids. He concludes by asking the questions: "Does the body endeavor to maintain as far as possible the acid-base equilibrium in the arterial blood and in the tissues, and in attempting this does it violate another principle of greater importance; namely, the proper balance of the inorganic constituents of its internal medium? . . . Has the correction of one balance lead to the disturbance of a more important one? And is the explanation of the symptoms of uremia to be found in a combination, in different proportions in different cases of these three important biologic equilibria?"

Syphilis of the Heart and Aorta.—SMITH (*Boston Med. and Surg. J.*, 1925, **193**, 387) summarizes very well indeed the present-day conception of a cardiologist as to the treatment of syphilis of the heart and aorta. His summary is conservative and agrees well with the opinion held by the majority of the men who are primarily interested

in cardiac conditions, although it differs considerably from the opinion of those who are interested primarily in the treatment of syphilis. The summary of the author's conception of the treatment of heart disease due to syphilis is as follows: Arsphenamin is valuable and should not be deleted from the treatment of cardiovascular syphilis, but mercury and iodids are the indispensable drugs in the treatment of these cases. Treatment should be begun with mercury and potassium iodid and should be continued some weeks, and then only after careful consideration of the clinical picture should arsphenamin be given. The initial dose should be very small and should be gradually increased to not more than 0.3 gm. If tolerated, repeated courses should be given, as in the treatment of syphilis generally. Arsenic is a dangerous drug with which to begin treatment. The danger increases in relation to the size of the dose and the organic changes present in the aorta and heart. No definite routine can be laid down or followed. In cases with marked renal insufficiency arsphenamin may be a safer drug than mercury. The author says that in the treatment of syphilis we should not forget that the patient has a damaged heart. General management of the case may be as important in determining the duration of life as the treatment of syphilis itself. Occasionally a case may be seen in such a desperate condition that one is justified in instituting the most intensive treatment in hopes of saving the patient's life. The author concludes with the statement that when the patient shows no systematic improvement with mercury and iodids he is extremely skeptical as to any benefit from arsphenamin.

Comparison of the Kahn with the Wassermann Test.—In the past few years a considerable amount of literature has accumulated concerning the value of the Kahn precipitation test for syphilis. The greater part of this work has confirmed Kahn's studies of his test and has shown that this test and the Wassermann test match each other very closely. FAUPEL (*Bull. Johns Hopkins Hosp.*, 1925, **37**, 170) has tabulated the findings of nine observers, which shows that they are for the most part very close indeed, averaging roundly about 90 per cent agreement. In her series of 400 examinations of the blood of syphilitics, she finds that 90 per cent showed absolute agreement; 3.8 per cent, relative agreement; 5 per cent, partial agreement; only 1 per cent showed absolute disagreement. The coëfficient of correlation of the heart series was found to be 0.79. Although this paper presents nothing new, it does give additional confirmatory evidence as to the value of this simple test for the presence or absence of syphilis. Papers such as this would help to establish the value of this test, and there can be no question but that it is a test of value. Kahn's precipitation test may be performed with a minimum amount of technical laboratory knowledge. A very small amount of equipment is necessary, and there is the additional advantage that the test may be performed in a very few minutes. As the author points out, this test can be well used in general dispensaries, and the results may be given before the patient has left. It may be carried out by practising physicians, as there is no necessity of keeping on hand rabbits nor an expensive incubator is not necessary. Incidentally, the author does not think the test is applicable to spinal fluids.

Carbohydrate Tolerance in Myxedema.—Hill, Brett and Smith (*Quart. J. Med.*, 1925, **18**, 327) draw the following conclusions from their studies of carbohydrate tolerance in thyroid disease: (1) Severe cases of exophthalmic goiter tend to have high and prolonged blood-sugar curves and to have glycosuria. (2) Myxedematous patients also give a blood-sugar curve which is higher and more prolonged than in normal persons; there is rarely glycosuria, and it is suggested that the renal threshold is raised in this condition. (3) The fasting level of blood sugar is in the majority of myxedema cases within normal limits. (4) No relationship between length of history of symptoms, clinical signs, the basal metabolic rate and the carbohydrate tolerance test could be established. (5) Thyroid extract does not raise the fasting level when myxedematous patients are treated; its general effect is to lower the blood sugar and to quick the curve. (6) The carbohydrate tolerance test is not so efficient a method of controlling the treatment of myxedematous patients as is the determination of the basal metabolic rate.

SURGERY

UNDER THE CHARGE OF

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Appendicitis in the Aged.—Maes (*New Orleans Med. and Surg. Jour.*, 1925, **78**, 117) writes that appendicular disease is relatively infrequent in patients over fifty years of age, but is accompanied by a very high mortality. After the thirtieth year the histology of the appendix, as of the tonsil, changes, and to this change may be attributed the early thrombophlebitis and the massive gangrene so frequently found at operation or at autopsy. The objective symptoms give no hint of the gravity of the intraäbdominal pathology and the naturally lowered resistance of elderly persons, plus organic diseases of the heart or kidneys, makes the prognosis always a serious one. Ileus, pyemia and septicemia are frequent complications. Early diagnosis and prompt treatment, in which free drainage is of prime importance, furnish the only possible means of reducing the mortality. Since the patients who develop fecal fistulæ usually recover, and since a late enterostomy usually does little good, it is suggested that a Pezzer catheter or a Paul tube be left in the cecum at the time of operation.

Postoperative Parotitis.—Simons and Rand (*New Orleans Med. and Surg. Jour.*, 1925, **78**, 129) say that every postoperative parotitis is a potentially lethal condition until it proves to be benign. This acute

inflammatory state occurs three to five days after operation and subsides in the same length of time. In acute circumscribed suppurative parotitis with local and systemic reactions intensified, pus can be pressed out of Stensen's duct in the absence of obstruction. Acute profuse suppurative parotitis is rare. Suppuration occurs in from thirty-six to forty-eight hours, with marked swelling of the face and severe general symptoms. Mortality is about 30 per cent. Gangrenous parotitis is very rare and almost always fatal. To await the spontaneous evolution of parotitis is to jeopardize life. When the condition is surgical early operation with free incision and open drainage is indicated. The greater the involvement of the face and neck structures, especially in gangrenous parotitis, the greater the need for thorough exposure.

Clinical and Surgical Aspects of Renal Neoplasms.—HYMAN (*Surg., Gynec. and Obst.*, 1925, **41**, 299) states that hypernephroma is the predominating type of kidney tumor. More than 50 per cent of his cases occurred during the fourth and fifth decades. The classical or primary symptoms of kidney neoplasms are pain, hematuria and tumor. Later on cachexia develops, metastases appear and evidences of venous stasis, the result of tumor compression, manifest themselves. Kidney tumors are extremely malignant. The author emphasizes the difficulty of early diagnosis, the disproportion between early symptomatology and pathologic findings and the importance of pyelographic data. While early diagnosis, based on classical symptoms does not necessarily indicate a favorable prognosis, extension into the vein does not render the prognosis hopeless. The ultimate mortality ranges between 65 and 75 per cent, and the only way to effect a reduction of this high rate at present would be to use the cystoscope and to make pyelograms, not alone in every case of hematuria, but in every case complaining of intractable sciatica and lumbago.

A Symposium on the Diagnosis and Treatment of Backache.—RUGH (*Therap. Gaz.*, 1925, **49**, 609) states that a study of roentgen-ray photographs, which included the lumbar, lumbosacral and sacroiliac regions, showed that there is some anatomical abnormality or variation in bony conformation present in about 85 per cent of apparently normal individuals. This includes irregularity in size, shape and relations of the processes, articulations and bodies of the vertebræ, the sacrum and the ilium. A firm strapping about the pelvis, keeping the straps between the iliac crest and the femoral trochanter is a very reliable diagnostic factor in all sacroiliac conditions, as it provides prompt relief, and a permanent cure may then be secured by a properly applied belt or corset. Tuberculosis of these bones is not uncommon and gives a history of a gradually progressive process with increasing disability and pain and the onset of deformity with frequently an accompanying abscess. The roentgen ray is diagnostic later in the process, but not early. Neoplasms in this region may be primary or secondary. The history and careful roentgen-ray studies are necessary to a diagnosis and the prognosis is bad. Surgery is useless. Pain in the middle of the back, over the sacrum and lumbosacral region, should always direct attention to the prostate gland and seminal vesicles.

Deep Roentgen-ray Therapy of Mammary Carcinoma.—EVANS and LEUCUTIA (*Am. Jour. Roentgenol.*, 1925, **14**, 135) say that the final outcome of mammary carcinoma depends on the manner of dissemination of the disease. Cancer spreads by embolic invasion of the lymph vessels and lymph glands, by extension, by continuity in the way of slow permeation of the lymph plexuses around the primary lesion and by embolic invasion of the blood stream. All operable carcinomas should be operated upon. The surgical procedure should be followed within ten to twelve days by postoperative roentgenotherapy. The site of the primary lesion, the adjacent glands and the microscopically permeated cancer area should be covered by radiation. All inoperable carcinomas should be treated by radiation. In instances apparent cures, and in all cases palliation and prolongation of life, are obtained. Cancer immunity exists. Radiation therapy may increase this defense mechanism of the organism.

Wound Healing in Syphilis.—MENNINGER (*Am. Jour. Syph.*, 1925, **3**, 445) claims that 22 surgical cases in which syphilis is present, as indicated by strongly positive Wassermann tests are here presented. In 4 cases receiving preoperative treatment, 3 presented some postoperative difficulty. All had positive Wassermann tests at the time of operation; despite the fact that they may have been treated, they cannot be operated upon with absolute impunity, although their postoperative courses may be uneventful. Untreated cases of active syphilis may develop postoperative difficulty in wound healing. The role played by syphilis is not determined. In some cases pyogenic bacteria of low virulence grow luxuriantly. In others there is a poor tendency to union without gross infection and in others there is no postoperative difficulty whatever.

The Use of Iodin in Goiter.—LAHEY (*Boston Med. and Surg. Jour.*, 1925, **11**, 487) writes that the use of iodin in the treatment of goiter has always been common. Iodin is useful, however in 2 pathologic thyroid states, 1 in regions where goiter is endemic and the iodin content of the drinking water is low, and as a measure to prepare toxic thyroid patients for operation. Its use as a prophylactic measure in the form of sodium iodid, 1 gr. per day for one week out of every six months, has been convincingly demonstrated by Kimball and Marine in their experiments with the school children of Akron, Ohio. The introduction of Lugol's solution by Dr. Henry S. Plummer as a method of preparation for operation in exophthalmic goiter marks a step of forward progress in the surgical management of this disease. It has practically eliminated preliminary pole ligation, and has made it possible to complete the operation of subtotal thyroidectomy in one stage upon a great majority of our patients.

The Value of Blood-pressure Determinations in Major Surgery.—ADAMS (*Texas Jour. Med.*, 1925, **21**, 241) states that surgery from the start tends to lower the blood pressure, and this depression in the average handicapped patient coming for operation begins from five to twenty minutes prior to any other symptom indicative of the approaching shocked state. The use of several large packs and loss of blood

will cause a temporary drop in the systolic and diastolic pressures. All three general anesthetics now in use—ether, nitrous oxid—oxygen and ethylene oxygen—cause a rise of blood pressure during the first fifteen minutes. But deep ether anesthesia continued for over one hour in any patient except the young adult of good cardiac compensation nearly always causes a distinct drop in both systolic and diastolic pressures and a well-recognized increase in pulse rate. It is true that ether is a socalled cardiac stimulant, but this is not the case when the amount is used that is necessary to produce complete and absolute relaxation. Nitrous oxid and ethylene seem to produce more gradual changes in pulse, respiration, systolic and diastolic pressures. Spinal anesthesia nearly always produces such an extreme drop in blood pressure that it is contraindicated in low-pressure cases. Novocain produces distinct drop in pressure when used in large amounts as a local anesthetic.

THERAPEUTICS

UNDER THE CHARGE OF

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The Action of the Intravenous Injection of a 40 Per Cent Solution of Urotropin.—Since Vogt (*Ztschr. f. Gynäk.*, 1921, vol. **49**) first advocated the intravenous injection of a 40 per cent solution of urotropin for the treatment of urinary retention this treatment appears to be the method of choice. RITSCHEL (*Deutsch. med. Wchnschr.*, 1925, **19**, 776) used this method in the treatment of 69 cases of urinary retention with success in 94 per cent of the cases treated. This method was used to give relief to patients with postoperative retention and also to relieve retention, several days after operation, which was of nervous origin. The usual procedure was to inject 5 cc. of the solution of urotropin on the evening after operation if necessary, and if no result followed to repeat the dose in one-half to two hours. If catheterization was necessary then the danger of infecting the bladder and urinary tract was minimized. Sterile solution of urotropin for intravenous injection are prepared by the firm of E. Schering, and sold in ampules containing 5 cc. This solution must be injected intravenously as intramuscular or subcutaneous injection is followed by painful infiltration.

Indications for the Intravenous Injection of Quinin Salts in Malaria.—Believing that the large variety of methods for the administration of quinin salts in the treatment of malaria indicates that the treatment of this disease is not grounded on a sufficient clinical or experimental basis, WIRSSALADSE (*Ztschr. f. klin. Med.*, 1925, **3–4**, 320) directs the attention of the practitioner to the intravenous injection of quinin solutions which was first advocated by Baccelli (*Priforma Medica*, 1890) for the treatment of pernicious malaria. In the treatment of malaria with this method Baccelli warned against generalization, and the author during the years 1920, 1921 and 1922 treated 164 of 952 patients who had malaria by this method, giving 821 intravenous injections,

and in three and a half years treated a total number of 216 malaria patients with 1141 intravenous injections of quinin. He uses a sterile solution of quinin dihydrochlorid, giving 0.5 to 1 gm., dissolved in 40 to 50 cc. of physiologic saline solution. This amount he injects very slowly into the median vein with aseptic technic. Under no circumstances does he use a stronger solution than 0.5 to 1 gm. dissolved in 40 to 50 cc. of physiologic salt solution. But this amount he may give two or three times or five to ten times, rarely as often as twenty times, to the same patient. Stronger solutions or larger amounts are dangerous, but using this small amount of a weak solution the author has seen neither local nor general disagreeable symptoms or complications after 1141 injections. Intravenous injection in all cases has given the best results in a clinical and parasitologic sense, and when all other methods of administration of quinin salts have been ineffective this method is most effective. However, it is by no means indicated in every case of malaria, and according to the author is only indicated in: (1) All pernicious forms of estivoautumnal malaria. (2) Tropical forms of malaria with many parasites in the blood although severe clinical symptoms are absent; such cases may develop severe symptoms at any time, and one or two intravenous injections are given and then other methods of giving quinin are instituted. (3) Acute forms of estivoautumnal malaria with severe symptoms but few parasites in the peripheral circulation; in such cases when one or two injections do not relieve the weakness of the patient he continues to give 1 gm. of quinin dihydrochlorid intravenously daily and 400 to 500 cc. of physiologic saline solution subcutaneously, or 0.5 gm. quinin dihydrochlorid intravenously and 0.5 gm. in 400 to 500 cc. of physiologic saline solution subcutaneously. (4) Quinin-fast forms of acute tertian, quartan or estivoautumnal malaria. (5) All patients who clinically or parasitologically have been found to be reinfected, as these cases often have a severe and protracted course. (6) Chronic and persistent recurrent cases of estivoautumnal, tertian or quartan. (7) Cases of malaria with chronic splenomegaly. The intravenous administration of quinin should be done only in the hospital, and as soon as a tangible result has been accomplished other methods of administration should be started. The author's working rules are: (1) Strict aseptic technic. (2) Cases must fit his classification. (3) Slow injection of the quinin solution. (4) Use of quinin dihydrochlorid in 1 to 2 per cent solution of physiologic saline, that is, 0.5 to 1 gm.; quinin in 50 cc. of saline. Contraindications to its use are arteriosclerosis, kidney disease, obesity, diabetes, lues and any other condition in which the intravenous injection of quinin might be harmful.

The Therapeutic Value of Coramin.—For the treatment of severe cases of collapse with low blood pressure and depressed respiration GUTH (*Therap. Gaz.*, 1925, **9**, 626) believes that coramin is superior to camphor. Coramin is a diethylamid of pyridin-beta-carbonic acid and is available in the form of solution for oral administration and in ampules of 1.1 cc. for injection. The highest effect was obtained in ten minutes after intravenous injection, and in thirty minutes when injected intramuscularly. The best results were obtained when both intravenous and intramuscular injections were given. No local or general toxic manifestations were noted from the use of coramin.

PEDIATRICS

UNDER THE CHARGE OF

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Diagnosis of Tuberculosis in Childhood.—SMITH (*Atlantic Med. J.*, 1925, **28**, 725), in his experience, found that tuberculosis in the bronchial nodes is the most frequent lesion encountered, and is at the same time very easily overlooked. When a child is seen who is pale and droopy, distinctly undernourished, or with a history of loss of weight, with bright eyes, long lashes and hairy arms and nape, tuberculosis should be suspected. A positive tuberculin test will show that the child harbors the bacillus. Then a temperature record should be kept, so that it might be ascertained if there is activity of the process. A careful physical examination, with special attention to the interscapular region, will often show a tracheal whisper to the fifth or sixth dorsal spine, and occasionally an asymmetrical upper line of pulmonary resonance. The lungs should also be examined with great care, especially in the nipple region and the axillæ, for persistent rales in these locations are suggestive as are signs of dry pleurisy or effusion. The superficial nodes must all be palpated, and the abdomen carefully searched for masses or ascites. The spines and bones must be thoroughly examined. Signs of early meningitis, such as crossness, headache and vomiting, must not be forgotten.

Pyloric Stenosis of Infants.—DAVISON (*Johns Hopkins Hosp. Bull.* 1925, **37**, 75) studied 60 cases, 32 of whom were treated medically and 28 surgically. He found that the frequency was highest among white, male, first-born infants of normal birth weight. The case fatality rate was highest among those who were not constipated, in whom the onset was sudden, who weighed less than 7 pounds at birth and on admission, and who had lost the most weight since birth. No fatalities occurred among infants who were overweight at birth or who had gained in weight between birth and admission to the hospital. The fact that the case fatality rate in the medical group was slightly under the rate in the surgical is no reason that all infants with pyloric stenosis should be treated medically, but it is a very good argument against operating on all of these patients as soon as the diagnosis is made, as has been recommended by some surgeons. By selective therapy, rather than by exclusively surgical or medical treatment, the total case fatality rate can be lowered.

Scarlet Fever: Etiology, Prevention by Immunization and Antitoxic Treatment.—PARK (*J. Am. Med. Assn.*, 1925, **85**, 1180) states that the antiscarlatinal serum produced by Moser and Savchenko produced the same therapeutic results as that now produced by the Dochez method or by the subcutaneous injection of known dose of toxin. The value of the earlier products was greatly handicapped by the lack of any

means, such as the Schultz-Charlton or the Dick methods, for estimating their antitoxic potency. Because of this lack of knowledge serum weak in antitoxin was undoubtedly given with disappointing results. The antitoxic serum should be given in sufficient amounts as early in the disease as possible. When thus given the result in most cases is strikingly favorable. The early use of antitoxin probably frequently prevents the development of complications. Antitoxin is useless after the rash has disappeared, and has no effect on later septic complications. In moderate cases it should be given intramuscularly. In severe or toxic cases it should be given intravenously. As a rule, a single dose of sufficient size is enough, but in severe cases in which the symptoms return a second dose in from twelve to twenty-four hours is often desirable. It is too early to state whether the serum should be given in very mild cases, since the serum sickness is often more annoying than the scarlet fever. The refined antitoxic serum produces fewer and less severe rashes than the unrefined, and should in time be the only preparation employed. A unit should be adopted, so that the results from different dosages may be compared. The one suggested at a recent meeting of immunologists in Washington seems to be suitable. One unit is defined as the amount of antitoxin that neutralizes 100 skin-test doses of Dick as determined by an intracutaneous test in man. A dosage between 2000 and 10,000 units will probably be sufficient in the great majority of cases. A few of the failures of antitoxin may be due to streptococci that produce other toxins than are neutralized by the antitoxin used. This is an interesting problem for future study. Whether it will be of marked advantage to combine an antimicrobial serum with the antitoxic serum is still doubtful. A serum of this class used in the past has given only doubtful results, but combined with antitoxin it may add to the benefit produced.

The Phenomena Concerned with Reactions following the Transfusion of Blood.—KORDENAT and SMITHIES (*J. Am. Med. Assn.*, 1925, **85**, 1193) observed that if whole blood is employed in transfusion, and if the donor blood is carefully selected posttransfusion reactions are relatively rare, and was less than 4 per cent in the series of the observers. Posttransfusion effects of a harmful type may be minimized if donors are selected not only with respect to their place in the arbitrary four groups of Moss's classification, but also when donor and recipient bloods are cross-grouped for estimation of their agglutinin-agglutinogen content. There are three types of posttransfusion effect: (1) The immediate, or hemolytic; (2) the delayed, apparently not hemolytic, but proteolytic; (3) the constitutional, or nonhemolytic. The subjective and objective phenomena of hemolysis can be explained by the effects of lysed blood on the peripheral capillary bed. The mechanism of these capillary responses is similar in kind, but greater in intensity, to peripheral vascular phenomena observed in Raynaud's disease, purpura and the like. The nonfulminant and delayed posttransfusion reactions are caused by anaphylactoid protein phenomena, but not necessarily of specific nature.

Energy Metabolism of Premature and Undersized Infants.—MARSH and MURLIN (*Am. J. Dis. Child.*, 1925, **30**, 310) determined the energy

metabolism in 82 observational periods on 21 premature and undersized infants, including 5 pairs of twins. The average basal respiratory quotient was low, 0.74, through the fifth day, rose to 0.79 on the sixth day, but never above this figure through the ninth day; whereas the quotient for a child in good nutritive condition, at least after the first week, should be about 0.85. The basal metabolism of these 21 infants averages 6.48 calories per hour, or 26.25 calories per square meter and 2.04 calories per kilogram per hour. On the basis of body surface, this is lower than the basal figure for full-term normal infants by 2.91 calories per hour. On the basis of the weight, it is slightly higher than for full-term infants, but is lower than would be expected if the metabolism per unit of surface were as high as it is for full-term babies. When the basal metabolism per square meter is averaged according to days of age there is a fluctuation during the first week, the lowest value coming on the seventh day with a higher value on the eighth and ninth days. Each day the metabolism is definitely lower than for the value obtained for normal babies born at term. Increases in heat production with activity varied from 2.5 per cent, with slight restlessness, to 40.3 per cent, when the child cried 39 per cent of the time. In a limited number of periods, and all on infants one month or less premature, the observation made previously for full-term babies, that is, crying 1 per cent of the time increase the metabolism 1 per cent, seems to hold fairly good. It seems impossible to obtain a basal period without food with which to compare a subsequent period with food for dynamic action. A few cases with variations in the amount of food fed to the same infant on the same day or on different days show a definite increase in heat production with more food, and when all the cases with small feedings are averaged and compared with the average of the cases following large feedings we find that an increase of 42.1 gm. of food increased the metabolism 5.19 calories per square meter per hour, or 21.3 per cent. The increased feedings on the basis of weight being nearly three times the increased feedings from which the dynamic action in full-term newborn infants were studied, it is not surprising to find the dynamic action nearly three times that noted in the previous study of these authors.

GYNECOLOGY

UNDER THE CHARGE OF

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Coincidence of Uterine Tumors.—The frequent coincidence of different tumors in the same uterus induced FRANKL (*Am. J. Obst. and Gynec.*, 1925, **9**, 745) to investigate the material of the First Gynecologic Clinic

of Vienna over a period of fifteen years. Among 1878 cases of myomata he found 46 sarcomata. He believes the relationship of these tumors may be: (*a*) The same uterus may contain a myoma and a sarcoma entirely independent of each other; (*b*) a myoma may be destroyed by a sarcoma which develops outside of it; (*c*) most frequently, the sarcoma develops within the myoma, growing from the center to the periphery, so that the myoma becomes destroyed and is replaced by the sarcoma. During the time that this series of 1878 cases of myoma were observed, in the same clinic there were 1036 cases of carcinoma, 919 of the cervix and 117 of the body. In 72 cases myoma and carcinoma were found in the same uterus. Among 919 cases of cervical cancer 62 uteri also contained myomata. Among 117 cases of body cancer 10 uteri also contained myomata. Basing the findings on myomata, we see that in 3.8 per cent of all myomata, carcinoma occurs at the same time. The number of body cancers, as related to the entire myoma material is 0.5 per cent. The number of cases of cervix cancer in relation to the entire myoma material is 3.3 per cent. Starting with carcinoma, the author found that in 6.8 per cent of the uterine cancers operated upon myoma was also present. These figures afford an entirely different picture from those given by other authors, whose data are based upon insufficient material, or are based on myoma examinations and therefore are not reliable. Their findings made it necessary to construct special theories to explain the pretended frequent occurrence of carcinoma of the uterine body, cases of myomata and the frequent occurrence of carcinoma in the myomatous uterus in general. But if we find that 6.8 per cent of all operated uterine cancers show myomata at the same time it is certainly no more frequent than myomata in the noncarcinomatous uterus. On the other hand, the frequency of 3.8 per cent of all myomatous uteri being carcinomatous at the same time is relatively high compared with the general frequency of cancer of the uterus. The author concludes that carcinoma of the body of the uterus is no more frequent in the myomatous uterus than is carcinoma of the cervix. In regard to the simultaneous occurrence of carcinoma and sarcoma in the same uterus, the author has seen 8 such cases, in most of which he believes that the tumors first existed side by side and later one grew through the other.

Pelvic Inflammatory Disease.—A statistical study of 294 cases of adnexal inflammation which were operated upon in the Gynecologic Division of the Breslau General Hospital during the past ten years has just been presented by MANNHEIM (*Zentralbl. f. Gynäk.*, 1925, **49**, 1471). In this series two-thirds of the cases were treated by means of a radical operation and one-third received a conservative operation. Forty-five per cent of the patients were married, widowed or divorced; 7 per cent were prostitutes; 48 per cent were single. Classified according to age, 56.4 per cent were under thirty years, 24.8 per cent were between thirty and thirty-nine years, while 18.8 per cent were forty years or older. Considering the etiology, 43 per cent were gonorrheal, 7 per cent were suspicious of gonorrhea, 5.8 per cent were septic or sapremic infection, 1.4 per cent were tuberculous, while in 43 per cent the etiology was unknown. In the series 228 patients were subjected to laparotomy, while 66 were operated upon *via* the vagina, but

it is significant to note that the percentage of vaginal operations has markedly decreased in the last few years. This is in keeping with the views of most gynecologists, since the abdominal operation is much more preferable than the vaginal except in the occasional rare case. Under the heading "conservative operation" are included such methods as simple incision of the tubes, release of adhesions, removal of one adnexa either alone or in combination with salpingostomy on the opposite tube, removal of both adnexa, conserving the uterus and one ovary, and finally conserving only one ovary. In spite of all these various conservative methods, an analysis of this series by years shows that the tendency in this clinic is to do more radical operations and fewer conservative ones every year. This is justified by the results obtained, since in the radical group there were 90 per cent cures, 0.5 per cent reoperated upon and 3 per cent mortality, while in the conservative group there were only 65 per cent cures, but 9 per cent reoperated upon and 3 per cent mortality. As a result of his study of the subject, the author concludes that the radical operation is to be preferred in most cases, as it will give a greater number of satisfactory end results, fewer cases which will require secondary operation and practically the same mortality as the conservative method, while the percentage of complications is the same in both methods.

Epithelioma of the Vulva.—It is a noteworthy fact, states SCHREINER (*Arch. Clin. Cancer Research*, 1925, **1**, 45), that the majority of gynecologists are extremely pessimistic as to the end results in the treatment of epithelioma of the vulva and clitoris. All forms of treatment in the past, whether by surgery, irradiation or coagulation, have yielded primary results that were gratifying, but leave much to be desired in the mitigation of suffering caused by recurrences in this class of patients. In a study of 31 cases of vulvar carcinoma at the State Institute for the Study of Malignant Disease, Buffalo, N. Y., it was found that the treatment with surface applications of radium and low-voltage Roentgen rays is inadequate and has been abandoned. The implantation of radium seeds in these lesions supplemented with high-voltage Roentgen rays has proven extremely painful to the patient, causing a great deal of suffering, especially from six to eight weeks after the treatment. The combination of implantation of the primary lesion with seeds and at times seed implantation in the metastases, with high-voltage Roentgen rays in addition, followed by electrocoagulation (endothermy) is the method of choice both for the comfort of the patient as well as the end results.

Cancer of the Vagina.—In a series of 33 cases of cancer of the vagina studied by SCHREINER (*Arch. Clin. Cancer Research*, 1925, **1**, 41) there were 29 epitheliomas and 4 adenocarcinomas. For purposes of study and treatment the cases were divided into two groups: Early cases, in which the tumor is confined to the mucous membrane of the vagina, more or less localized, and far-advanced cases, which involve a large portion of the vaginal wall and have infiltrated the rectal or bladder walls, or metastasized in the groin or broad ligaments. The surgical treatment of cancer of the vagina offers practically nothing on account of the anatomic difficulties, so any form of treatment that offers a

possible relief, whether only symptomatic or only palliative for a time, is of value. The results in this series were extremely poor because the majority of the cases were so far advanced. The effort was made to administer as much radiation against the lesion as possible, keeping in mind the dangers of fistula formation. The dosage of radium in these cases varied from 150 mc. hrs. to 2500 mc. hrs., filtered through 2 mm. brass and 1 mm. rubber supplemented with high-voltage Roentgen rays and radium packs applied over the symphysis or perineum sufficient to bring the total dose up to 120 to 135 per cent, 3 cm. from the tubes. In this series 4 out of 8 cases in Group I have been clinically well for periods varying from two months to two years and eight months. Two of 21 far-advanced cases have been well, 1 for three years and the other for one year and seven months. In the 4 cases of adenocarcinoma of the vagina 3 died from the disease and 1 has improved. The author believes that the application of radium against the lesion in the vagina, supplemented with high voltage Roentgen ray, offers more than any other known treatment for cancer of the vagina.

OTO–RHINO–LARYNGOLOGY

UNDER THE CHARGE OF

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Cerebrospinal Fluid as Index of Otorhinogenic Intracranial Complications.—Describing the normal spinal fluid as a clear, colorless, sterile fluid, containing sugar but no globulin, and in the adult not more than 8 lymphocytes per c.mm., YERGER (*Jour. Am. Med. Assn.*, 1925, **85**, 424) reported the results of a study on 155 cases of meningitis, 43 cases of lateral sinus thrombosis, 35 cases of brain abscess, 8 cases of labyrinthitis, 4 cases of extradural abscess, 2 cases of cavernous sinus thrombosis and 1 case of subdural abscess. It was learned that although the cerebrospinal fluid is a reliable index of some of the intracranial complications of otorhinogenic origin, even being pathognomonic in some instances, it may be misleading, and should not be relied on to the exclusion of other dependable clinical signs indicative of intracranial involvement. The knowledge obtained from examination of the cerebrospinal fluid may be of value either in a positive or a negative manner. A negative finding at once differentiates a meningismus from meningitis, and it usually eliminates meningitis, brain abscess, subdural and extradural abscess. However, one negative finding in a case of threatened or manifest intracranial complication should not be considered final. A sterile cerebrospinal fluid with a low cell count (from 25 to 250) excludes a suppurative meningitis, but throws suspicion on the presence of an extradural or brain abscess; in a medium cell count (from 250 to 2500) one should suspect a subdural or brain abscess or meningitis; but in the high (over 5000) and very

high (over 10,000) cell count a diffuse suppurative meningitis is usually present. A diffuse meningitis is considered clinically proved when bacteria are found in the cerebrospinal fluid. In a circumscribed meningitis, serous or suppurative, of otorhinogenic origin the cerebrospinal fluid returns to normal after the removal of the focus of infection, as extradural or brain abscess; but when drainage is insufficient it does not return to normal, and when complicated by an acute diffuse purulent meningitis there occurs a sudden and marked increase in the polymorphonuclear leukocytes, with or without the association of bacteria. Diffuse septic (bacterial) suppurative meningitis is associated with a high polymorphonuclear cell count plus the invading bacteria; it is frequently the sole otitic intracranial complication, but it may be associated with brain abscess or septic sinus thrombosis as a terminal complication.

Treatment of Fibromas of the Nasopharynx: Report of Thirty-two Cases.—NEW and FIGI (*Ann. Otol., Rhinol and Laryngol.*, 1925, **34**, 191) reported the effects of treatment on hard fibromas which occurred in the nasopharynges of 32 patients. The ages varied from ten to thirty-one years, the average being eighteen and a half years. Twenty-nine (90.6 per cent) were less than twenty-five years of age at the time of examination, and 3 (9.3 per cent) were between twenty-seven and thirty-one years. The activity of the tumor seemed to be directly related to the age of the patient, although the fact that operations had been performed in many instances made it hard to determine this point. Twenty-eight of the tumors occurred in males and 4 in females. The average age of the males was nineteen years and that of the females fifteen years. The duration of symptoms previous to examination was from two months to six years. Five patients had had symptoms for less than one year, 9 for more than two years. Twenty-three of the 32 patients had been operated on from one to twelve times prior to their examination at the Mayo Clinic. While the authors recognize that the "Type of treatment to be selected for new growths is that which will give the best end results in each particular case," and classify the therapeutic procedures into three groups: (1) Surgical, (2) cautery or diathermy and (3) radium and roentgen ray; they feel that in nasopharyngeal fibromata radium is the treatment of choice. Before radium was used (1910 to 1915) 8 patients in the series were observed, 5 of whom were operated upon by the avulsion method. Of these 2 died and no trace of the other 3 could be found. From 1915 to 1924 24 patients with fibroma of the nasopharynx were examined. Twenty-three were treated with radium, which was applied by any of three methods, with a T-shaped lead applicator, by inserting steel points containing radium emanation or the element directly into the tumor or by implanting emanation seeds in the neoplastic tissue. The dosage depended largely upon the size of the tumor. It was found that by the use of radium the usual operative mortality was eliminated. In most of the cases the tumor cleared up entirely, and in others it was held in check during its period of activity. That the treatment, and not the natural regression of the tumor, was the important factor in the cure, the authors mention that 11 (73.3 per cent) of patients were less than twenty-three years of age when cured, and 4 (26.6 per cent) more than twenty-three years of age when cured.

RADIOLOGY

UNDER THE CHARGE OF

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Chronic Infection of the Gastrointestinal Tract: Its Roentgen-ray Manifestations.—There is a tendency of roentgenologists, according to EASTMOND (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 541), to disregard the manifestations of gastrointestinal disorders when they involve anything but the detection of ulcer, cancer and diseases of the gallbladder or appendix. There are important manifestations of chronic infection that should be recognized. There are abnormal appearances seen on the lesser curvature of the stomach that are neither ulcer nor malignancy, but occur in the form of more or less localized filling defects. These show the presence of congestion, round-cell infiltration and fibrosis, and although it is not an erosive condition the author prefers to call it ulcerative gastritis. There is also the condition called "stiffening," characterized by having no localized serrations or defects in the marginal filling of the stomach, but the pyloric extremity for a distance of 2 or 3 inches is smooth, contracted and shows alteration in the character of the peristaltic waves. In the duodenum are seen many deformities, nonulcerative in character, due to the same process seen in the stomach, namely, a chronic round-cell infiltration with fibrosis and diminishing of the elasticity of the bowel. There may be small craters in the mucosa of the first portion of the duodenum, and these should be called ulcerative duodenitis. The adhesions so often considered secondary to pericholecystitis are really due to the duodenitis. In the second portion of the duodenum there is a coëxistence of disease which is very common, and here adhesions result from a periduodenitis as well as a cholecystitis. In the ileum, besides the numerous conditions recognized, there is an intrinsic ileitis that has been overlooked, which is also a condition of congestion, with round-cell infiltration, fibrosis and more or less cicatricial narrowing. The cecum shows changes of infiltrative or sclerotic type and may include the ileocecal valve, causing incompetency of the valve. The colon also shows chronic sclerotic changes, and it is recognized by the lack of elasticity or irregular contraction, most commonly seen in the sigmoid.

An Analysis of Bone and Joint Lesions of Known Syphilitic Origin.—In view of the great confusion existing in regard to bone lesions, especially of syphilitic origin, CAMPBELL (*Radiology*, 1925, **5**, 122) has analyzed a number of known syphilitic bones and joints. Syphilis of bones and joints is usually found only in the tertiary stage. The records show that trauma may induce typical luetic lesions in syphilitic subjects. The syphilitic process is first proliferative (periostitis), a precursor to the later or degenerative (osteomyelitic) stage. Some

cases were found to have more than one focus. In the roentgenography of bone syphilis, bear in mind that the distribution may be local or diffuse in any part of the bone, or there may be multiple foci in two or more bones; that the first change is a fuzzy proliferation of periosteum, sometimes stratified; that the bone blister may occur and also form a bone ulcer; that there may be a fine bone formation called "lace work;" that the bone cortex may enlarge and encroach upon or obliterate the medulla. The degenerative or osteomyelitic stage gives massive enlargement of the bone, with areas of increased opacity alternating with areas of destruction, without atrophy. The opacity so characteristic of syphilis is an attempt at hypertrophy. Hypertrophy of the cortex is very common in syphilis and should always be looked for when syphilis is suspected. In syphilitic arthritis there may be changes in the soft structures before the bone shows any lesion. Bone syphilis usually shows gross changes before the subjective symptoms appear, while in joint syphilis the symptoms of pain, muscular spasm and disability are far less than the physical and roentgenologic signs would indicate. Taking this fact and the blood Wassermann into consideration, the author believes the following changes to be most suggestive: An increase in density of one of the bones of the articulations; extra-articular proliferation of the periosteum of one of the bones forming the articulation; punched-out area on lateral or medial aspects; fuzziness of joint surface; large opaque area within the cancellous bone near the articular surface and extensive bone destruction without atrophy. Joint syphilis tends to spontaneous recovery without ankylosis. In congenital syphilis the joint lesion was found more to be common than the bone lesion. The author reported 33 cases of joint lesions with a positive Wassermann, but without any clinical or roentgenologic symptoms of syphilis, which were unresponsive to antisyphilitic treatment. Therefore, the fact that a Wassermann is positive does not prove that all bone and joint lesions present are syphilitic.

Myeloid Myelomata.—Moore (*Radiology*, 1925, **5**, 18) reports 4 cases of myelogenic tumors classified as: (1) Chloroma of myeloid type, and considered a myelocytoma; (2) plasma-cell type, or plasmocytoma; (3) 2 cases like the second group, but differing in many ways. The plasmocytoma was the ordinary and usual form of multiple medullary myeloma, and had as its characteristics the production of ovoid or rounded rarefied areas in bones, giving the appearance of being expanded from within. In the second case, that of multiple myeloma of plasma-cell type, the process seemed to be confined mostly to the long bones, and showed no sign of bone production or expansion. The changes in the bone consisted of small circular rarefied areas of sharp outline and little tendency to become confluent, suggesting the existence of multiple discrete small tumors. The blood count and smear was not unusual, except that there were from 3 to 7 per cent myelocytes present. The histologic report of the bone marrow showed a strong suggestion of erythroblastic origin for the tumor, but it was finally considered a plasma-cell type of myeloma. The third case showed successive development of tumors of the clavicle, forehead and right sacroiliac region. These were treated by deep Roentgen-ray

therapy, to which they responded very readily. Roentgen-ray examination at this time revealed pathology in many bones, characterized by a rarefaction and destruction of bone, but the outline of the rarefied areas was not clear cut; and, where multiple, these tumors tended to fuse. Later a tumor mass was removed from the abdominal wall which was found to be a myeloid myeloma of plasma-cell type. After reëntry to the hospital several times, receiving relief from symptoms by deep Roentgen ray, the patient finally became much worse and died. The fourth case was that of a man coming to the hospital with a pathologic fracture of the humerus and a white blood cell count of 85,100, of which 22 per cent were myelocytes, mostly basophilic. There was a large mass in the humerus, but no other bone lesions. The arm was amputated and the pathologic report was myeloma. The patient was treated for leukemia with benzol and Roentgen radiation with much benefit. He reëntered the hospital many times with new masses and bone involvement, which for a while responded to treatment, but finally overwhelmed the patient, causing death. The clinical and postmortem diagnosis of this case was leukemia with peculiar manifestations, yet it was undoubtedly a chloroma of the myeloid type presenting malignant tendencies, and therefore is a unique case. The author considers these 4 cases as four separate and distinct malignant conditions of bone marrow that are distinct from leukemias, and are not sarcomatous but of hematogenic origin.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Relation of Social Work to Psychiatry.—TRUIT (*Am. J. Psychiat.*, 1925, **5**, 103) feels that social workers make more contacts with psychiatric cases in all stages of development than do psychiatrists in private or institutional practice. A greater coöperation is urged between psychiatrist and social workers in order that the former may become familiar with the social aspects while the latter grasps some of the psychiatric aspects. The proper coöperation should bring about a more comprehensive social psychiatry.

Studies of Gastric Secretion and Motility in Mental Patients.—The study is a continuation of work reported in 1923, in which it was tentatively concluded that depressing emotions inhibited gastric and even duodenal secretion; that mental exaltation seemed to favor gastric secretion; that somatic and hypochrondriac delusions bore no relation to secretory variation. In all, 191 women were studied, presenting a great variety of reactions from depression to elation; some nonaffected cases were also included. Of the whole series 13 per cent

were overweight, 31 per cent normal and 56 per cent underweight. FARR, LUEDERS and BOND (*Am. J. Psychiat.*, 1925, **5**, 93) conclude, however, that malnutrition was not correlated with any of the effective groups *per se*. The effective groups showed basal metabolism scattered evenly on either side of normal, while the noneffective patients tended to have low basal metabolism. Seventy per cent of the patients with elongated or ptosed stomachs were underweight, while only 30 per cent of those with normally located stomachs were thus classified. They conclude, however, that the position of the stomach is primarily an expression of habitus and related only secondarily to nutrition. Position and atony seem to have less relation to emptying time of stomach than would be expected. Colon emptying was slightly delayed in depressed patients, but in such small degree as to warrant caution in conclusions. Sixty per cent of patients with hyperacidity or hypoacidity were underweight. Forty per cent of patients with achlorhydria were underweight. In 50 per cent of achlorhydria cases pernicious or severe anemias, gallstone disease, carcinoma, nephritis, etc., were present, and in 25 per cent more of this group some of these diseases were possibly present. Only 7 per cent of the hyperchlorhydria or hypochlorhydria cases had evidence of associated organic diseases. More of the depressed cases tend to have low gastric acidity or achlorhydria. A very high acidity was found in some patients after excitement incident to doing the tests. The authors feel that acute emotions (anger, fear, etc.) probably affect gastric secretion more than "habitual feeling tone." A chart is given which gives all the data.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Analysis of the Fecal Flora in Thirty-three Cases of Pernicious Anemia.—MOENCH, KAHN and TORREY (*Jour. Infect. Dis.*, 1925, **37**, 161) say that a bacteriologic analysis of seventy-two stool specimens from 33 cases of pernicious anemia of various durations showed in practically every case an unusually large number of viable organisms, of which Bacillus coli, streptococci, Bacillus welchii and, at times, Bacillus acidophilus, were the most prominent types. These findings indicated that the flora of the large intestine is of an actively growing, nonproteolytic, fermentative type. The most significant feature revealed by these examinations would seem to be the uniformly high counts for Bacillus coli and Bacillus welchii. The numbers of both

these organisms averaged much higher than for normal persons or for other pathologic conditions. Although streptococci were also very numerous, they conformed to the normal intestinal types, no representative of the hemolytic group being encountered. Pure cultures of Bacillus welchii strains were isolated from 26 of these cases, and subjected to differential tests. Representatives of the four fermentative types of Simond were encountered, but Type I occurred with the greatest frequency (50 per cent). These several strains differed also in the amount of hemolysin produced. Although most of them were strongly hemolytic, it could not be said that they exhibited in general greater potency in this respect than did strains from normal human intestines. All of the strains tested showed a high degree of pathogenicity, but this is also frequently true for strains from normal sources. It would seem, then, that if these intestinal strains of Bacillus welchii are to be brought into etiologic relationship to pernicious anemia it must be on the basis of their excessive numbers and activities, particularly at levels of the intestine where absorption is active and where they are not commonly found only in negligible numbers. In view of Seyderhelm's finding that the flora of the large intestine tends to invade the small intestine in this disease, there is some ground for the latter supposition. Speculation is offered as to the possible significance of active growth of Bacillus welchii at the higher levels of the intestine in the production of the pernicious anemia syndrome in view of its well-known capacity to elaborate a potent hemolysin, an irritating acid and neurotoxic substances.

Bacterial Factors in Pyorrhea Alveolaris: IV. Micrococcus Gazogenes, a Minute Gram-negative, Nonsporulating Anaërobe Prevalent in Human Saliva.—HALL and HOWITT (*Jour. Infect. Dis.*, 1925, **37**, 112) emphasize the frequent occurrence in human saliva of a minute, Gram-negative, nonsporulating, obligate anaërobe. This organism is mainly responsible for the abundant gas generally seen in primary brain medium cultures from unheated saliva. It is identical with the socalled Staphylococcus parvulus (Veillon) recently recovered by Holman and Krock, which they thought resembled Bacillus pneumosintes in filtrability. The authors, however, disagree both as to its nomenclature and its ability to pass through carefully controlled Mandler filters. Micrococcus gazogenes is a minute diplococcus less than 0.5 micron in length and breadth, Gram-negative, nonsporulating, nonmotile and obligately anaërobic. These properties have caused it to be overlooked in most of the modern work on the mouth flora. It is nonpathogenic directly for rabbits, guinea pigs and mice, but it appears to reduce the resistance of rabbits toward other pathogenic microbes. Ten rabbits, immunized by intravenous injection of live cultures, produced powerful agglutinins (all over 1 to 10,000) which distinguished two serologic groups. Group A contained twenty-two strains; Group B, two strains. Holman's cultures fell into Group A. Normal rabbits harbor Micrococcus gazogenes, yet produce no agglutinins except under inoculation, but human beings not infrequently produce low-grade agglutinating serums (1 to 40). The strongest serum came from persons free or practically free from gingival lesions, suggesting an immunologic factor relating to this organism in pyorrhea alveolaris.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 19, 1925

Electrokinetic Behavior of Mammalian Serous Membranes.—STUART MUDD (from the Laboratories of the Rockefeller Institute for Medical Research). Glands may be regarded from one point of view as systems in which a liquid secretion is transported through the capillary interstices between colloidal molecules, micellæ and cells. The capillary interstices are simultaneously traversed by an electric current, the action current of the gland. Does the electric current in such a system influence the movement of liquid? Is the action current too small to have an effect? Is the concentration of salts in the body fluids so high as to abolish electrokinetic effects, which have ordinarily been observed in systems of lower electrolyte concentration? In considering these questions I have had recourse to mammalian serous membranes, which have sufficient similarity from a physical-chemical point of view, but are easier to work with. The membrane is attached over the mouth of the electrode vessel and is bathed inside and out with the perfusing liquid. Current is passed and the rise and fall of the meniscus in the electrode vessel is observed. All liquids tested, whose reaction has been more alkaline than pH 5.9 have streamed through the serosæ toward the cathode. Each membrane has a characteristic hydrogen-ion reversal point, however, on the acid side of which streaming is to the anode, as indicated in communications already published (*J. Gen. Physiol.*, 1925, **7**, 389 and **9**, 73). The rate of electroendosmotic flow has been found to be proportional to the current strength. The plots of current strengths against volumes of liquid transported in unit time are straight lines *passing through the origin*, indicating that there is no threshold value below which current is ineffective. Any current flow whatever tends to produce liquid flow. The plots of rate of liquid flow against specific resistances of the perfusing buffers do show minimal rates with buffers whose electrolyte concentration is between M/6 and M/10; the actual mean rate of flow when living mesenteries were bathed in whole serum was found to be 0.29 c.mm. per minute per milliampère. The glandular action current then is *not negligible*. Whether it is relatively unimportant or the controlling factor in glandular secretion can only be determined by further experiment.

Estimations of Glomerular Capillary Pressure in the Frog.—J. M. HAYMAN (from the Laboratory of Pharmacology of the University of Pennsylvania). Accurate information concerning the blood pressure in the capillaries in the glomeruli of the kidney is essential for a satisfactory understanding of the processes which take place there. Such information has not hitherto been available. Recent work in this laboratory has shown that the minute structures in the kidney of the living frog may be made accessible both to direct observation and

instrumental manipulation. In the work here reported blood pressures in the glomerular capillaries and afferent arterioles of the frog's kidney have been estimated. Frogs were prepared according to the method of Richards and Schmidt (*Am. J. Physiol.*, 1924, **71**, 178) for observation of the renal circulation. A capillary pipette filled with colored salt solution, attached to a Harvard manometer and a device for regulating the pressure, was introduced into Bowman's space. The lumen of the tubule was occluded by pressure. By increasing the pressure within the capsule flow through the capillary tuft could be slowed or stopped. The highest intracapsular pressure at which flow was continuous through at least one capillary throughout the cardiac cycle was taken as equivalent to capillary pressure; that at which a few corpuscles just entered the tuft with each systole, as equivalent to the systolic pressure in the afferent artery. Aortic blood pressure was determined at the same time by another Harvard manometer connected with a cannula in one aorta. Pressures have been measured in the surviving kidneys of frogs during perfusion with oxygenated Hamburger's solution, and also in kidneys of living frogs in which the blood circulation was normal. In general, the pressures in the afferent artery and glomerular capillaries varied directly with aortic pressure. In one perfusion experiment pressure in the aorta was 22 cm. of water; in the afferent arteriole, 18 cm.; in the glomerular capillaries, 10 cm. In another the pressures were 33, 26 and 17 cm. respectively; in a third, 46, 40 and 24 cm. In 94 estimations of glomerular capillary pressure in kidneys with normal circulation the estimations varied at different blood pressures from 4 to 40 cm. of water; the average, 18.6 cm.; 60 of the estimations have been between 11 and 25 cm. of water. In 1 experiment systolic pressure in the aorta was 24 cm. of water; in the afferent arteriole, 19 cm.; in the glomerular capillaries, 15 cm. In another, 34, 28 and 19 cm. respectively, and in another 49, 45 and 30 cm. In the perfusion experiments the pressure in the afferent arteriole averaged 86 per cent of aortic; in the glomerular capillaries, 52 per cent; in living frogs the averages were 86 and 51 per cent respectively. These estimations are appreciably higher than those found by Hill and McQueen (*Brit. J. Exp. Path.*, 1921, **2**, 205) by a less direct method.

Allergic Irritability.—Paul Lewis and Dorothy Loomis (from the Department of Animal Pathology of the Rockefeller Institute for Medical Research, Princeton, N. J.). In furtherance of our observations on inheritance as an influence in the natural resistance of guinea pigs to tuberculosis infection we have sought to determine the nature of at least some of the qualities involved. Our attention of late has been directed particularly toward those principles which are basic in the modern conception of acquired immunity and which may in some measure be fundamental in natural resistance. The natural approach to these questions, in part, is through a study of the humoral factors in acquired immunity. The antibodies are particularly accessible to observation, are most definitely understood, and hence have served as our starting-point. In view of the consensus of opinion that antibodies actively created in one generation are transmitted to the next only by the female line, and in a purely passive and temporary way, it is plain that any factor involving the activity of these principles must be transmitted in the inheritance as a latent capacity to react to antigenic stimuli

and as a latent capacity only. Experiments intended to measure these latent capacities directly, and in the strict sense of the words, have not yet succeeded. We have, however, been able to study the response to certain stimuli which appear to be directed at the latent capacities, and whose effects are indirectly evidenced by specific antibody production when appropriate antigens are administered. Active infection with the tubercle bacillus at certain stages of its progress in guinea pigs and rabbits is the most effective stimulant we have encountered. Infection with Bacillus abortus and with a streptococcus of guinea-pig origin act in the same direction, but less effectively. Likewise treatment with dead tubercle bacilli and with the vital stains trypan blue and trypan red are effective. Under the influence of these stimuli antisheep hemolytic amboceptor and antityphoid agglutinin are produced in the usual manner as evidenced by the curves of formation from day to day. The absolute amounts may be twenty-fold those produced in the absence of such stimuli, and the differences have been maintained over periods sufficing for a series of immunizing treatments. As a result we have been able to secure concentrations of antisheep amboceptor in the guinea pig which have exceeded by ten or more times under stimulation, the maximum amount secured by a comparable series of injections with erythrocytes alone. In this response to these stimuli the inbred families of guinea pigs with which we have dealt appear to differ. In other words, the capacity to react to these indirect stimuli is transmitted in variable degree in the inheritance. Our title requires explanation. In use the phrases "capacity to be immunized," "latent capacity for antibody production," and so forth, have proved cumbersome and not wholly accurate. It has seemed to be better from the academic point of view to recall that it has been customary to say that an animal once subjected to a foreign protein, or once infected or vaccinated with a particular microörganism, is rendered allergic, or put into a state of allergy with reference to that protein or that microörganism. Academically considered, and with relation to physiology, the production of immunity or of hypersensitiveness involves the conception of stimulation, which again is a reflection of a fundamental irritability. We are thus led to the use of the term "allergic irritability" as designating a general characteristic of the animal, on the basis of which it reacts to stimuli of the antigenic class, whether these be helpful, injurious or indifferent to bodily health. Those interested will find a more complete discussion of these questions in the papers of: Wright and Lewis (*Am. Naturalist*, 1921, **55**, 20) and Lewis and Loomis (*J. Exp. Med.*, 1924, **40**, 503; 1925, **41**, 327), and in papers shortly to be published.

Studies of Gastric Juice in Children with Gastrostomies: Colorimetric and Electrometric Determination of the Hydrogen-ion Concentration.—G. KAHN and J. STOKES (from the Department of Pediatrics of the University of Pennsylvania). The object of the present study was to decide the best technic for determining the hydrogen-ion concentration of gastric juice as a preliminary to its application in a study of gastric secretion in infancy and childhood. In a comparison of the electrometric and colorimetric methods, as described by Clark, 100 specimens of gastric contents were examined. In the colorimetric method the dyes, thymol blue, bromphenol blue, methyl red, brom-

cresol purple and phenol red were used. The specimens selected covered thoroughly the range of pH 1.8. Considerable differences were found between the electrometric and colorimetric results on the same specimen. Below pH 3.5 the discrepancy between the two methods was generally less than 0.5 pH, while above 3.5 the differences were much more marked, amounting frequently to 1 pH, or at times even up to 2 pH. For this reason the colorimetric method was considered to be unreliable, unless correction could be made for the above differences. With the hope of eliminating the effects of protein and salts on the dye used, correction of the colorimetric readings was first attempted by diluting the gastric contents. This was unsuccessful. The method of dialysis, as used by Levy, Rowntree and Marriott, and Dale and Evans, was then applied to eliminate the effect of protein on the dyes. Three cubic centimeters of the gastric contents in a collodion sac was dialyzed against 3 cc. of physiologic saline solution for one hour, and the dialysate then tested colorimetrically. Results much more consistent with the electrometric determinations on the unaltered specimens were thus obtained, with a maximum difference between the two of 0.3 pH. It is therefore recommended, where electrometric determination of the CH of gastric juice is not feasible, that colorimetric determination on the dialyzed specimen be carried out. The second part of the problem concerned the evaluation of the stomach tube in the ordinary methods of gastric analysis. The subjects for the study were children with gastric fistulas which had been made because of acid or lye strictures of the esophagus. By dilatation with bougie through the gastrostomy the esophagus was rendered normally patent, thus affording entrance into the stomach both through the fistula and through the esophagus. Specimens obtained through the fistula showed consistently much more free and total acid and a higher CH than those obtained by stomach tube through the esophagus. These findings are best explained as the results of the increase of mucin and saliva in the gastric contents incident to the gagging and retching caused by the passage of the stomach tube.

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